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BILATERAL LOSS OF VISION FROM CEREBRAL INFARCTION

BY

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INTRODUCTION

Loss of vision in both half-fields as the result of cerebral infarction is a rare occurrence. Hemianopia is, of course, not uncommon in cases of hemiplegia from infarction, and a subsequent vascular lesion in the other hemisphere may cause loss of the remaining visual fields. Such cases we do not propose to consider in this paper, which will be devoted to the study of bilateral visual loss from infarction of the occipital lobes. In these cases there is as a rule no hemiplegia, hemianæsthesia or aphasia, except when symptoms of this kind have resulted from a lesion independent of that responsible for the loss of vision, as proved by the time of onset or pathological age of the lesion at autopsy. We have been mainly interested in cases in which there has apparently been simultaneous loss of vision in both half-fields. The qualification is necessary because a patient may have a hemianopia without being aware of it, and the onset of blindness may then be due not to simultaneous bilateral infarction but to successive lesions. Nevertheless in a number of cases the clinical evidence makes it highly probable that both occipital lobes were involved at the same time. The origin of these simultaneous and symmetrical lesions offers an interesting problem. A further problem of anatomical and physiological interest arises from the observation that in many cases, whether the double hemianopia is simultaneous or successive, there is sparing or recovery of vision in certain areas of the field.

In addition to the visual loss other symptoms are sometimes present, such as spatial disorientation, visual hallucinations and denial of blindness. The clinical picture, therefore, may show variations which deserve study.

REVIEW OF THE LITERATURE

The earlier case reports date from a time when the anatomy of vision was imperfectly known, and it was important for this

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reason simply to record the fact of visual loss associated with softening limited to the occipital lobes. Some of them, however, contain clinical observations which are relevant to the problems we shall discuss. We have therefore included in our summary of the literature all the cases we have been able to find in which loss of vision has been correlated with the post-mortem observation of bilateral occipital lobe infarction. We have added a number in which there was no post-mortem examination but the clinical evidence appears adequate.

Cases with Post-mortem Examination

In very few of these cases is there anything more than a description of the lesions in the occipital lobes as they appeared to the naked eye, this being of value in establishing the cause of the visual loss, without offering any explanation either of the pattern of any vision that remained or the cause of the infarction. There is seldom any detailed account of the state of the basal arteries. Where these have been mentioned we have included the data given. In all other cases the reader may assume that they are lacking.

Berger (1885) recorded the case of a man aged 71 who complained suddenly of giddiness and visual impairment interfering with reading and writing. From these symptoms he recovered. Seven months later there was a sudden onset of vertigo with blindness. He did not lose his senses but was confused and dysphasic. Examined a few hours later he had no perception of light but the fundi and pupillary reactions were normal. A fuller examination next day confirmed these observations. There was no dysphasia but a slight right hemiparesis which subsequently improved. He remained completely blind until his death six weeks after the onset. Post-mortem examination showed atheroma of the basal arteries with old thrombosis of the right internal carotoid artery and more recent thrombosis of the left vertebral artery. There was recent softening of the whole left occipital lobe as far as the parieto-occipital fissure. In the right occipital lobe on its outer surface there was a circumscribed area of softening about the size of a 10 pfennig piece in the middle part of the first convolution. This appeared to be quite superficial, and no other area of softening was found in the right occipital lobe. A separate area of softening was present in the left temporal lobe. In this case, therefore, no adequate explanation was discovered for the loss of vision in the left half-fields.

Von Monakow (1885) published the case of a woman who was admitted to hospital, aged 43, on account of dementia. Five years later she suddenly lost her senses and on regaining consciousness after a few hours was blind and unable to stand. After four days she had some perception of light. The fundi were normal and the pupils throughout contracted well to light. Two months later she had a series of epileptic seizures,

but after this episode there was no alteration in the physical signs. She had visual hallucinations and did not seem to be fully aware of her blindness, which later was complete. She died three months after the onset of the illness, and the post-mortem examination revealed extensive softening of both occipital lobes involving the cuneus and lingual gyrus on both sides. There were no other lesions in the brain.

Bouveret (1887) reported a typical case, his observations being more complete than most of those subsequently recorded. His patient was a road-worker aged 72, who had previously been in good health and had had no previous defect of vision. Having gone to work as usual, he was found standing with his arms clasped round a tree. He was confused, but with help was able to walk unsteadily to hospital. When examined next day he was confused and incoherent but with no dysphasia or other abnormal physical signs except that he was completely blind. The fundi were normal and the pupils contracted normally to light. His pulse was irregular. Twelve days later he developed a slight left hemiparesis. This was followed by pulmonary infection and he died seventeen days after the onset of his illness.

The post-mortem examination showed atheroma of the basal arteries, but the basilar artery was patent. Both posterior cerebral arteries were occluded by organized thrombus; on the left beginning at the level of the first bifurcation and extending into its branches on the internal and inferior aspects of the brain: on the right beginning 1·5 cm. from the basilar bifurcation and also extending into the peripheral branches.

Macroscopic examination of the brain revealed softening of the whole of the internal and inferior surfaces of both occipital lobes with the exception of the extreme posterior extremities. On the right the softening had extended forward to involve the posterior third of the inner and under surfaces of the temporal lobe. The eyes were removed and examined and the retinæ found normal, as also were the optic nerves. There was left ventricular hypertrophy and ante-mortem thrombus in the left auricle, and in the apex of the left ventricle, the latter being soft and friable. Bouveret concluded that the occlusion of the posterior cerebral arteries was embolic from the heart, but was puzzled by the simultaneous occurrence.

Oulmont (1889) reported a case with softening confined to the occipital lobes. This patient, a man aged 77, had complained of headache and tingling in his limbs for fifteen days and then suddenly was found confused and blind. The pupils are said to have been dilated and almost immobile. There is no report on the fundi.

Förster (1890) recorded a case of successive double hemianopia, the second lesion occurring five years after the first, in a man then aged 49. He first had a right hemianopia of sudden onset with sparing of central vision of one or two degrees. The second episode developed in the course of three days, after which he had to be led around like someone

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totally blind. On examination six weeks later his behaviour was that of a blind person. The fundi were normal, as also the pupillary reactions to light. Förster then found that although the patient could scarcely decipher the letters of J.20 he could read correctly with either eye ordinary writing and small type. Perimetry showed that only a very small part of the central field remained. This was confined to a semi-circular area below the horizontal meridian extending to a few degrees in all directions from the fixation point. He also had spatial disorientation, loss of visual imagery and loss of colour vision. This appears to be the first case in which the ability to see small objects, but not large ones, was correctly interpreted in terms of the visual field loss, and this particular defect distinguished from those due to visual agnosia. The brain of this patient was later examined by Sachs and the findings are discussed in some detail by Henschen (1900) with figures. The visual field defect had not changed before death. There was infarction involving the medial aspects of both occipital lobes with small islands of cortex preserved at the posterior extremities of the calcarine fissures. From this Sachs deduced correctly that macular vision was represented at the posterior occipital poles, though Henschen would not accept this, arguing that the optic radiations must have been completely destroyed posteriorly and that the case supported his own view that central vision was represented in the anterior part of the calcarine fissure.

The case recorded by Dejerine and Vialet (1893) is a classic. This was a man admitted to the Bicetre at the age of 64. He had been in normal health until shortly before his admission, when he began to be suspicious, accusing his wife of infidelity and refusing to let her see visitors. At this time he also had frequent attacks of vertigo and complained of impaired vision, having to give up his work as a tailor. Two years later he had two separate attacks in which he lost consciousness for half an hour. Following this he was uncertain in walking but had no paralysis or dysphasia. There was no further development until three years later he suddenly lost his vision without paralysis or loss of consciousness. He was repeatedly examined during the subsequent two years. Although he saw nothing he would not admit blindness. When he was shown objects and asked to name them he did so without hesitation, but wrongly. When convinced of his error he would make an excuse, saying that he had a tear in his eye. His behaviour in general was that of a blind person, making use of touch and hearing to remedy his defect. It was found, however, that he could distinguish light from darkness in a small sector in the upper part of his left visual fields. The fundi were normal, and the pupils contracted normally to light. No abnormalities were noted in the nervous system except in his gait, which was that of a blind person with some additional disturbance of equilibrium. His condition did not change until he died of pneumonia five years later after the onset of blindness.

The post-mortem findings, so far as the brain is concerned, were fully reported as "Cas Bras" by Dejerine (1901). What is of particular importance in this case is that while naked-eye inspection revealed softening of an extent which would not in the light of modern knowledge have accounted for the blindness, serial sections adequately explained it. In the right hemisphere the cuneus was destroyed, including the upper lip of the calcarine fissure, but its lower lip was intact. Below this there was softening of the lingual gyrus. Sections revealed that these two areas of softening were connected, undercutting the area of surviving cortex. In the left hemisphere superficial inspection showed destruction only of the posterior part of the lingual gyrus and adjacent lip of the calcarine fissure, but the sections revealed that the lesion had extended deeply to destroy the terminal part of the whole optic radiation.

Peters (1896) recorded the case of a man aged 68 who suddenly noticed impaired vision and disequilibrium. He was found to have a left hemianopia with visual disorientation. Six months later, although there had been no further ictus it was discovered that the only part of the visual fields remaining was a central circular area extending about 5 degrees from the fixation points. This area subsequently expanded to about 12 degrees. Colour vision was preserved. Spatial disorientation persisted. The fundi and pupillary reactions were normal. Death occurred two years after the first onset. Post-mortem the relevant finding was infarction of both occipital lobes.

Lunz (1897) reported a women aged 55 who had sudden giddiness with brief loss of senses, a transient left hemiparesis and almost complete blindness. There was some return of vision so that she was able to get about. Seven months after this she had a further attack of vertigo with deterioration of vision and when examined two weeks later was blind with normal fundi and pupillary reactions, and was confused. Post-mortem examination revealed softening of both occipital lobes. Small scattered areas of softening about the size of a pea were found in the region of the basal ganglia on both sides. The cerebral arteries were atheromatous.

Kustermann (1897) reported (Case 1) a man aged 51 who complained of headache and impaired vision and was found to have a right hemianopia. A few days later he lost his senses and on recovery was found to have constriction of the left half-field. Subsequently he had several attacks of vertigo, and after one of these complained that he could not see. The fundi and pupillary reactions were normal. Vision was lost except in the periphery of the left upper quadrants. There was spatial disorientation and loss of visual imagery. Death occurred after a convulsion ten days after the onset of blindness. The post-mortem examination showed occlusion of the calcarine artery at its origin on both

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sides with destruction by softening of the medial surface of both occipital lobes involving cuneus and lingual gyrus.

Meyer (1900) reported a man who at the age of 56 had a sudden right hemianopia with transient paresis of the right arm. Four years later he suddenly became blind without other symptoms. Vision partially recovered but was again lost suddenly four years later without any other symptoms. When examined next day he was found to be blind with normal fundi and pupillary reactions. Five days later he had recovered a small area of central vision in both fields and with corrected vision could read single letters of the smallest print. He showed visual disorientation and loss of visual imagery. His condition remained unchanged to the time of his death one year later. At the post-mortem examination there were old areas of infarction in both occipital lobes, the rest of the brain being normal. The basal arteries were atheromatous.

Raviart and Cannac (1909) recorded a man aged 58 who had been blind for two years and showed severe intellectual deterioration. Post-mortem there was softening of both occipital lobes, the lingual gyrus being chiefly involved, the cunei relatively intact.

Marie and Léri (1911) recorded 3 cases of bilateral visual loss from infarction but with meagre clinical details. All their patients were demented and no clinical history was obtainable. In 2 cases there was some preservation of central vision in the right half-fields, but perimetry was impossible. The softening was in all cases confined to the occipital lobes and involved what is now known to be the visual cortex with sparing of part of the left visual cortex in the cases with some preservation of vision. Marie and Léri observed that the dementia in these patients was of no ordinary kind. Those who had some preservation of vision behaved like blind persons for certain actions, but for others like seeing persons. You would think they were quite blind, but they would deceive you by recognizing an object even of very small size. This the observers interpreted as due partly to the preservation only of a small area of central vision, partly to visual agnosia. The patients were aware of visual disorientation and described it. Their visual memories, however, were preserved. Although there was also disorientation in time and defective memory for recent events, they were less demented than they appeared, but even those who had some preservation of vision appeared in their behaviour more disabled by their loss than a patient with total blindness of peripheral origin.

Bramwell and others (1915) recorded the case of a man who at the age of 43 had an illness thought to be nephritis, in the course of which he suddenly lost his eyesight and had a series of epileptic fits. When he recovered consciousness he remained blind but in the course of the next three years recovered some central vision. His visual acuity was at this time recorded as R 5/18 partly and L 3/18 partly, and central colour vision

as good. He was able to see small objects such as a pin on the floor, but failed to recognize large objects. Perimetry showed preservation of a few degrees of central vision in the right half-fields. He died at the age of 71 and the brain was examined by Shaw Bolton. There was old infarction of both occipital lobes, but histological study revealed in Bolton's opinion only a small lesion of the posterior end of the right calcarine cortex with no involvement of the rest of the visual cortex or of the optic radiations. Bolton concluded that the loss of vision in the centre of the left visual fields was caused by the lesion described, and that the case proved that panoramic, as opposed to central, vision must be subserved by association fibres outside the striate zone. This case presents a puzzle which we will deal with in the discussion.

Mella (1922) reported the case of a hypertensive male aged 55, who after an attack of gastro-enteritis experienced sudden loss of vision. He is recorded to have appreciated hand movements only. Post-mortem examination eight months later showed softening of both occipital lobes.

Lagrange and others (1929) record the case of a man aged 65 who became suddenly blind with brief loss of consciousness. On examination he was blind but without any sensation of being in darkness. The fundi and pupillary reactions were normal, but blinking to menace was lost. He was under observation for three months, during which he had visual hallucinations and denied blindness. At post-mortem there was softening in the areas supplied by both posterior cerebral arteries, the striate cortex being destroyed on both sides.

Rimbaud and others (1932) report a man of 58 admitted to hospital with the complaint of episodes of clouding of vision and headaches. No abnormal signs were found, but there is no note of the visual fields. Seven months later he suddenly became blind. He was observed to be totally blind with normal fundi, and a normal contraction of the pupils to light. At post-mortem there was total destruction by softening of the medial surface of both occipital lobes. There was no trace remaining of the calcarine fissures or the convolutions separated by them. The lesions were symmetrical, not extending on to the convexity. Following the course of the posterior cerebral arteries from their origin to the point of penetration into the cerebral substance there were plaques of atheroma partly obliterating the lumen, especially, on both sides, at the level of the branch destined for the visual cortex.

The paper by Holmes (1934) is of outstanding importance, perimetric observation being correlated with a detailed examination of the visual cortex. We have been able to examine the original case notes of this patient at the National Hospital, Queen Square, and have extracted some details of the history which do not appear in Holmes' paper but are relevant to the subsequent discussion. An intelligent man of 47 on

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January 19, 1928, picked up a telegram and found difficulty in reading it, because all the letters seemed to run into one another. He attended an ophthalmic hospital with no relief, and the difficulty in reading continued for a week. Shortly after this he began to have attacks of vertigo two or three times a day, each lasting about half a minute. Throughout February, March and April the attacks of vertigo continued, and he became aware that his fields of vision were becoming more and more restricted. He likened this to a fan being gradually closed up. By April he was beginning to knock into things indifferently on either side. At this time the giddy attacks were sometimes accompanied by a feeling of numbness starting in the right side of the head and spreading rapidly down the arm, trunk and leg on that side. The whole episode lasted about half a minute. Between the end of April and his admission to hospital in August the attacks of giddiness and numbness had become much less frequent, and he did not think his vision had deteriorated farther. On examination, apart from his vision the only abnormalities found were a slight weakness of the right lower face and right half of the palate. Corrected visual acuity was 6/12 in each eye. The fundi were normal and the pupils contracted normally to light. The visual fields showed preservation only of an area extending from the fixation points upwards on either side of the vertical meridian in the shape of a wedge with its apex at the fixation point and its base at the periphery. He died in October following a negative exploration for a pituitary tumour. Post-mortem there was softening, obvious to the naked eye, of the cortex in the region of the calcarine fissure in both hemispheres. Microscopic examination of serial sections revealed destruction on both sides of all the striate cortex except a small area below the posterior extremity of the calcarine fissure, and extending forward from this a strip corresponding with the lower border of the striate area and reaching to its anterior end. The lesions on the two sides were very nearly symmetrical. There were several areas of softening in the cortex of the cerebellum, and one between the right pyramid and inferior olive. The basilar artery was very much thickened by an almost uniform ring of atheroma. It was, however, patent, and the posterior cerebral arteries at their origin looked healthy. The left internal carotid artery was almost completely occluded by a patch of atheroma on one side.

Hemphill (1941) reported 2 cases. The first, a man of 60, had been a patient in a mental hospital for four years after attempted suicide. He then complained of sudden headache and said he was blind. He did not lose his senses but for a few hours was confused and disoriented. A week later he was able to distinguish light and darkness in a small area in the lower quadrants of the left visual field. Eight months later he suddenly became unconscious and died in ten minutes. Post-mortem there was old softening of both occipital lobes. The basilar artery at its termination was occluded by an old, organized clot which extended into both posterior

cerebral arteries. There was a large recent hæmorrhage in the right half of the cerebellum.

The second patient, a man aged 63, became suddenly confused on the day before admission. He was disoriented in time and space but could both see and hear. Four months later he had a stroke with brief loss of consciousness, from which he emerged with right hemiplegia and complete blindness. The fundi and pupillary contraction to light were normal. The blink reflex to menace was absent. Two months later he had three attacks of unconsciousness with twitching of the left limbs and died. Post-mortem there was old softening of both occipital lobes and a separate area of softening in the left middle cerebral territory. A clot occluded the right posterior cerebral artery and extended across the Circle of Willis to occlude the left posterior cerebral and middle cerebral arteries.

Riley and others (1943) recorded 4 cases. Their Case 2 was that of a 49-year-old man who six years previously had been observed to show some intellectual deterioration with dysarthria, an ataxic gait, and extensor plantar responses. At this time he also had a right homonymous hemianopia. When admitted to hospital the physical signs, apart from vision, were as already described. The visual fields were extremely constricted with only central vision intact. The fundi and pupils were normal. The post-mortem examination showed softening of both occipital lobes with sparing of the posterior poles. There were also old areas of cortical softening in both lateral lobes of the cerebellum in the distribution of the superior cerebellar arteries.

Their Case 3 was a man aged 51, said to have lost his vision gradually two years previously. He was admitted to hospital for a recent left hemiplegia. On examination he was confused and blind with normal fundi and pupils. Post-mortem there was old infarction of both occipital lobes, recent infarction of the right middle cerebral territory, and an old area of cortical softening in the left lobe of the cerebellum. All the arteries of the Circle of Willis and the posterior cerebrals showed severe atheroma.

Their Case 4, a man aged 44, had had an episode of severe vertigo ten years previously. Shortly before his admission to hospital he began to have attacks of dysarthria and drowsiness, and subsequently attacks of temporary loss of vision and confusion. On examination he was blind with normal fundi and pupils. Post mortem there was thrombosis of the left vertebral and posterior cerebral arteries. The right vertebral artery was congenitally small. The basilar artery showed severe atheroma. There were areas of old and recent softening in both occipital lobes, and an old area of softening in the pons.

Their Case 5 was a hypertensive man of 62 who for one year had suffered from episodic vertigo and more recently attacks of numbness in the right and occasionally the left limbs. There had been progressive

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visual failure for three months. On examination vision was lost with the exception of a narrow concentric zone in the right lower quadrants. Post mortem there was softening of both occipital lobes with destruction of the lingual gyri extending into the calcarine fissures. The right vertebral, basilar and both posterior cerebral arteries showed severe atheroma. The left vertebral artery was rudimentary.

Biemond (1951) records the case of a man aged 56 who for some years had suffered from headaches and dizziness and fleeing impairment of vision for which he was admitted to hospital. Five days later, after a period of intense headache, he became totally blind, but on the following day vision returned and he had a right homonymous hemianopia, which cleared up in three days. A month later he again experienced severe headache and impaired vision, developed a quadriplegia with signs of brain-stem involvement, and shortly afterwards died. At post-mortem there were areas of softening in both occipital lobes in the area striata, and in the right cerebellar hemisphere. In the middle of the basilar artery an old, not completely occluding, thrombus was found, upon which a recent thrombus had been deposited, completely occluding the lumen.

Lawrence (1952) reported the case of a man aged 47 who complained of progressive loss of vision over a period of ten days, together with occipital headache. Vision was reduced to light-perception peripherally. The fundi and pupillary reactions were normal. Vision improved and at the end of a week he could count fingers. He then suddenly developed the signs of what would appear to have been a brain-stem lesion. Post-mortem nearly symmetrical areas of softening were found in both occipital lobes involving the posterior poles and medial aspects, including the visual area of both lobes.

Millikan and Siekert (1955) record the case of a woman aged 67 who was admitted to hospital with a history of transient episodes of vertigo, and of weakness and numbness of the right and left limbs, and dimness of vision. While in hospital the patient complained one morning that she could not see. She was found to have gross impairment of vision without complete loss. Vision subsequently improved. There are no perimetric observations. A few weeks later she died with symptoms of a pontine infarction. Post-mortem there is recorded old thrombus in both posterior cerebral arteries with bilateral infarcts in the occipital lobes and recent thrombosis of the basilar artery extending into the right vertebral artery with infarction of the pons.

Kearns, Wagener and Millikan (1955, Case 2) record the case of a woman aged 69 who in the course of three weeks had several attacks of dizziness with numbness of her left face and "half her vision blurred." When first examined her visual fields were full to confrontation. In the next two weeks her attacks continued and she developed severe visual impairment. At this time the whole of both visual fields were lost except

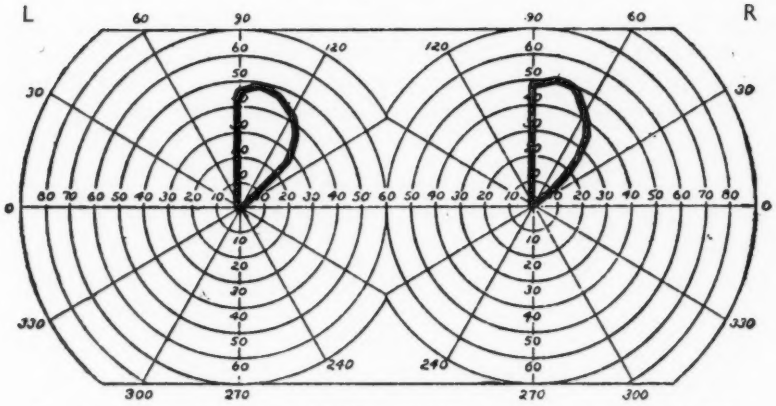

FIG. 1.—Kearns, Wagener and Millikan (1955). *Case* 2. Perimeter 35/330.

for a sector-shaped area in the right upper quadrants adjacent to the vertical meridian and reaching centrally to the fixation point (fig. 1). Sixteen days later this area had enlarged to include the greater part of the fields above the horizontal meridian. Shortly afterwards she developed a quadriplegia and died. Post-mortem there was a massive pulmonary embolism, recent infarction of the pons and multiple infarctions in both occipital lobes. There was thrombosis of the right vertebral artery extending up into the basilar.

Cases without Post-mortem Examination

Some of the cases recorded are of doubtful value owing to the absence of recorded observations of the fundi, and pupillary contraction to light, and others for lack of detail in the clinical history. We have selected those in which the diagnosis of bilateral occipital infarction appears valid, and the clinical features are of particular interest.

Schweigger (1891) reported a man aged 73 who suddenly developed a left hemianopia without other symptoms or signs. A year later in exactly the same manner he lost the other half-field. He felt himself quite blind and gave that impression, but a small central field was still present. At a distance of 3–4 metres he could see the face of his wall clock and discern the figures. There was no spatial disorientation.

Groenouw (1892) recorded the case of a professor aged 58 who on returning home one evening was noticed to be stumbling around. There was a transient left hemiparesis, and left hemianopia which persisted, but did not prevent his return to work. Eight months later in the course of three days he became drowsy and disoriented with gross impairment of vision. Groenouw examined him one month after this and found slight weakness of the left arm but nothing else except visual impairment.

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Visual acuity (corrected) was 6/6 in each eye. The fundi and pupillary reactions were normal. The visual fields showed an incomplete left hemianopia together with a left paracentral scotoma and loss of the right inferior quadrants (fig. 2). The fundi and pupillary reactions were

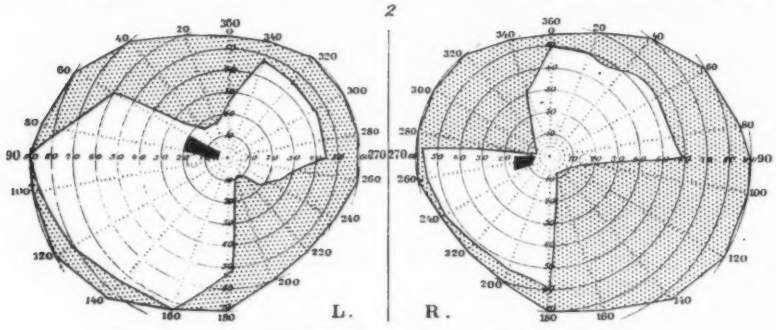

FIG. 2.—Groenouw (1892). Perimeter 5 mm. white object.

normal. There was visual disorientation but no loss of colour vision. He subsequently improved and returned to his work but still suffered from spatial disorientation, being unable when he visited a restaurant to find his way out.

Knies (1896) observed a man aged 64 who three years previously had experienced a sudden impairment of vision. Four weeks before he was examined he woke in the morning to find he could no longer see things in his room. He was somewhat confused for a few days. On examination there was loss of all the visual fields except for a central semilunar area above the horizontal meridian extending 10 degrees to 15 degrees from the fixation point. There was no spatial disorientation and he was able to read and write and get about by himself.

Allyn (1896) records the case of a man aged 49 who suddenly became blind. After a few minutes there was partial recovery of vision. Examined three weeks later, his fields showed a left hemianopia with sparing of central vision to about 5 degrees. Six months later he suddenly lost consciousness, and when he regained it was again blind. On this occasion there was again partial return of vision. Perimetry showed preservation of a small central area in both visual fields with sector-shaped extensions in the right upper and left lower quadrants, these in each instance being adjacent to the vertical meridian (fig. 3).

Kustermann (1897) observed (Case 2) a woman aged 35 who suddenly lost her senses, was subsequently convulsed and on recovery was blind. Later there was some return of vision. On examination eight months later the fundi and pupillary reactions were normal. The visual fields showed preservation of a small area of central vision with an extension

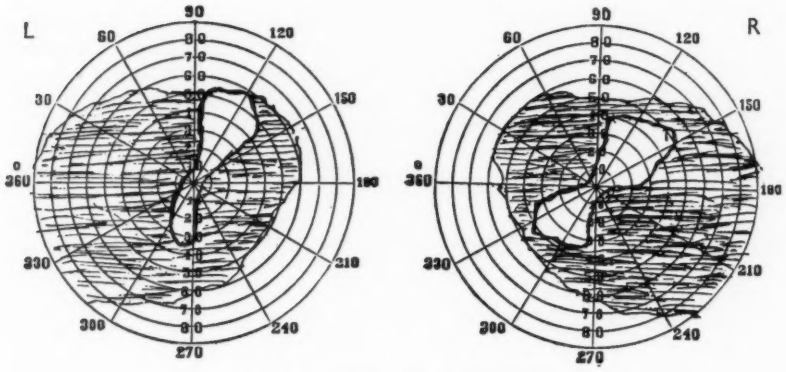

FIG. 3.—Allyn (1896). Perimeter.

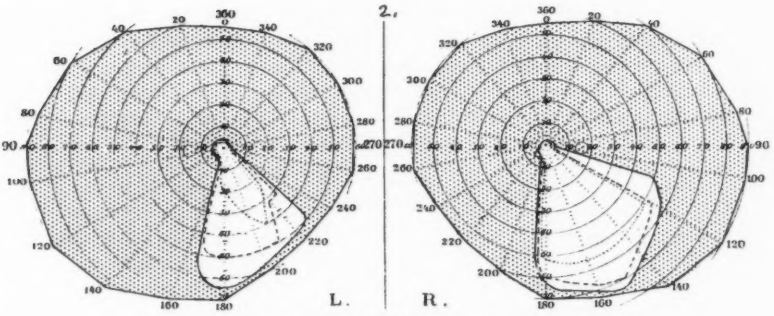

FIG. 4.—Kustermann (1897). *Case* 2. Perimeter.

into the right lower quadrants adjacent to the vertical meridian (fig. 4). She was able to read and write but suffered in some degree from spatial disorientation.

Jacqueau (1900, Case 1) observed a man aged 64 eight hours after the sudden onset of total blindness. At this time there had been some return of vision. He was able to see the head of a glass pin held in his hand though everything around it was black. The fundi and pupils were normal. At the end of forty-eight hours he had only a complete right hemianopia with a little sparing of the central portion of the field.

His second case was that of a man aged 70 who one year previously had suddenly become blind with no recovery. There was no perception of light. The fundi and pupillary reactions were normal.

Raymond, Lejonne and Galezowski (1906) recorded the case of a man aged 57 whose illness had begun six months previously with an attack of vertigo. In the subsequent three weeks there were further attacks of

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vertigo followed by the sudden onset of complete blindness without loss of consciousness. In the course of the next two weeks there was some recovery of vision, followed by the sudden onset of confusion and complete blindness. Again there was some recovery. On examination there were a slight dementia and a moderate degree of spastic weakness of the bulbar supplied muscles and all four limbs, the plantar responses being flexor. Vision was restricted to a small area in the centre of the left half-fields extending to about 10 degrees from the fixation point. The fundi and pupillary reactions were normal. Colour vision was preserved in this area.

Worster-Drought (1928) reported 2 cases with perimetric observations. One of these subsequently died and the brain was examined by the late Dr. Carnegie Dickson. Dr. Worster-Drought has generously allowed us to report this case in full, and its details will appear later. His second case was that of a woman aged 72 who for the past two years had complained at times of temporarily blurred vision and occasional dizziness. One afternoon she complained of occipital headache and then asked her daughter to light the gas as it had become so dark. It was then discovered that she was almost totally blind. Perimetry showed that vision in both fields was restricted to a circular area extending to 10 degrees from the fixation point. The fundi and pupillary reactions were normal. The blood pressures were 240 mm. systolic; 120 mm. diastolic.

Terrien (1938) reported a man (age not stated) who had a sudden attack of giddiness and was found to have a left hemianopia without other abnormal signs. Eight months later he had a further attack and was then found to have lost all vision except for a small central area in both fields. Terrien observed "Il lui est absolument impossible de se diriger du fait de la réduction à une petite aire centrale et de la perte de la totalité des champs visuels a l'exception de cette petite aire."

McDonald (1943) recorded the case of a man aged 49 who a few days after a coronary thrombosis found he could not see to the right. He returned to work without any further complaint, but two years later, while talking to a neighbour, suddenly became completely blind for a brief period. When his vision returned he felt he was looking through a narrow tube. Perimetry showed preservation of central vision in both fields to a distance of 10 degrees around the fixation point, together with partial preservation of a narrow sector in the right lower field adjacent to the vertical meridian (fig. 5).

Ross (1949) observed a hypertensive male aged 61 who experienced sudden headache and loss of vision with partial recovery. He was found to have lost the whole of both visual fields except for a central circular area whose circumference was at about 10 degrees from the fixation point, and extending downwards from this a small sector in the left lower quadrants adjacent to the vertical meridian. His visual acuity was 20/20 in each eye (fig. 6).

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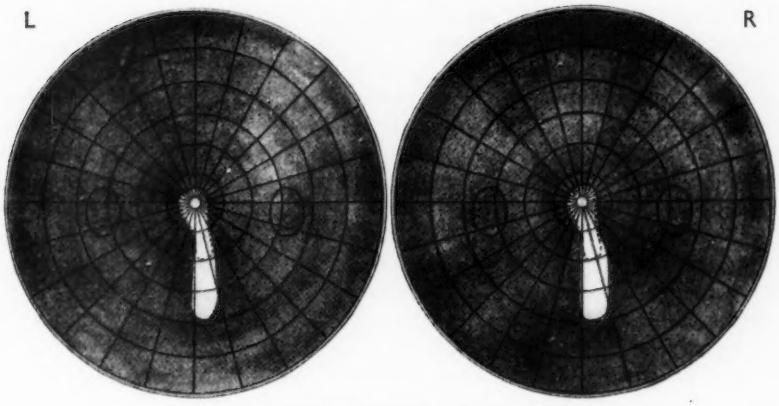

FIG. 5.—McDonald (1943). Screen 1/1,000.

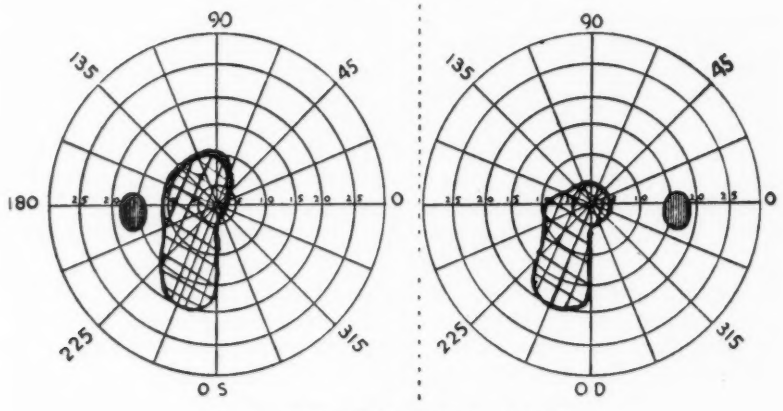

FIG. 6.—Ross (1949). Screen. 6/1,000.

Steiner (1951) recorded a hypertensive woman aged 57 who woke one morning finding herself unable to get about alone owing to impaired vision. Her visual fields showed preservation of a central circular area extending to about 10 degrees. With appropriate lenses she was able to read J.1 with either eye. Perimetry was repeated at intervals of three months for the next two and a half years and showed no change.

Wagman (1952) observed a hypertensive male aged 77 who suddenly became confused and blind. His pupils contracted normally to light, the fundi were normal and there were no other abnormal signs. He remained totally blind until he died suddenly in coma two years later.

Reese (1954) reported 4 cases with presumed softening of the occipital

cortex on both sides. In his Case 10 there had been a previous vascular lesion causing a left hemiparesis. Two years later the patient, a woman of 48, suddenly became blind. The visual fields were limited to a few degrees about the fixation point in each eye. Signs of aortic and mitral valvular disease were present. His Case 11 was that of a man who experienced sudden loss of vision while at dinner with partial recovery in the next three weeks. Perimetry showed that vision was preserved only in a half-circle extending 10 degrees to the right of the fixation point. His Case 13 was that of a woman aged 58 with a history of auricular fibrillation, who suddenly became blind while dressing. After a few minutes there was momentary improvement and then again loss, but with some return of central vision. Perimetry showed that vision was limited to a few degrees from the fixation point in the left lower quadrants. His Case 14 was that of a man aged 60 who experienced sudden loss of vision while driving his car. He was admitted to hospital next day. He could distinguish only light from darkness and had to be led about for eight days. Examined nineteen months later he showed only a left hemianopia.

Kearns, Wagener and Millikan (1955, Case 1) record a man aged 59 who while feeding his chickens suddenly became blind. He was somewhat confused and attributed his blindness to lightning, having got up earlier in the morning to watch a thunderstorm. When examined in hospital next day he was confused and virtually blind, apparently appreciating hand movements vaguely in the extreme periphery of the right half-fields. The fundi were normal and the pupils contracted normally to light. There was horizontal nystagmus to right and left, and both plantar responses were extensor, but there were no other abnormal signs. He was transferred to a mental hospital owing to his confusion.

Their third case was that of a man aged 70 who three years previously had had a coronary thrombosis. He was admitted to hospital, having six days before felt unsteady on his feet and generally weak, with difficulty in focusing his vision. From these symptoms he rapidly recovered, but then again complained of impaired vision and was readmitted in a state of impaired consciousness with a right facial weakness and bilateral extensor plantar responses. From this state he recovered and was then found to be almost blind, so that he had to be led around, though he did not fully appreciate his disability. Perimetry revealed preservation of a half-circle of vision above the horizontal meridian extending to about 15 degrees from the fixation points (fig. 7).

Further Observations

The rarity of these cases is indicated by the fact that although one of us has been especially interested in them for over twenty years the opportunity for a post-mortem examination has never come his way. Through the generosity of friends and colleagues we have been able to

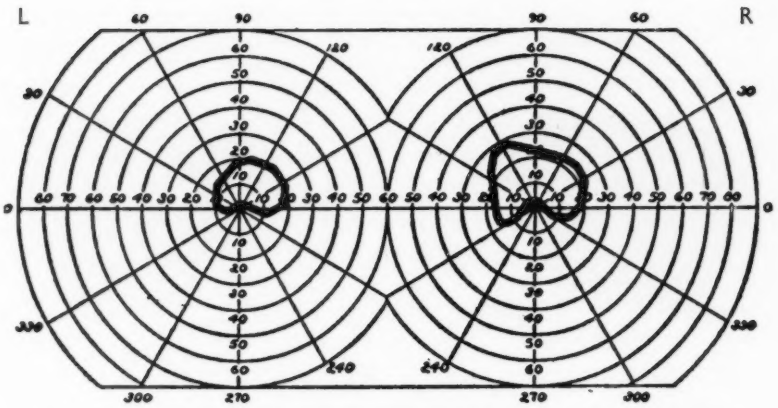

FIG. 7.—Kearns, Wagener and Millikan (1955) *Case* 3. Perimeter 35/330.

collect four examples of the syndrome with pathological confirmation. one of these has been briefly reported before (Symonds, 1948) and is now published *in extenso*, and another has been the subject of a previous clinical report (Worster-Drought, 1928). We have added 5 cases in which there was no post-mortem examination, but the clinical evidence was satisfactory.

Case 1.—This case was reported by Worster-Drought (1928). He has kindly provided us with his original notes together with the report of a post-mortem examination made at a later date by Dr. Carnegie Dickson.

W. P., male aged 48, presented himself at the West End Hospital for Nervous Diseases in 1928 with the complaint of defective vision and occasional dizziness.

One evening in February 1919 he found on coming out of a shop that he walked into people on his left side. On the following day he experienced slight right-sided occipital headache and occasional dizziness. There were no further symptoms for nine months. Then one evening when walking in the street he suddenly realized that he could see scarcely anything at all. He felt somewhat dazed and dizzy but had no other symptoms. His condition had remained substantially the same since that time. The diagnosis of hysteria had been made at another hospital, and he was treated by psychotherapy without improvement. On examination the fundi were normal and the pupils contracted normally to direct light and consensually and on accommodation convergence. Occasional nystagmoid jerks were observed on lateral deviation of the eyes. Apart from this no abnormalities were observed in the neurological examination with the exception of the visual fields (fig. 8). These had been examined on many occasions during the past eight years and had always been found substantially the same. Visual acuity was 6/9 in each eye.

In November 1933 he was admitted to the West End Hospital under Dr. Worster-Drought with the story that on the previous day he had been found unconscious in his bedroom during the morning. The relatives stated that three months previously there had been an episode of loss of memory. A week before his admission he had seemed "far off" and strange in his manner. He was stuporose on admission and died ten days later.

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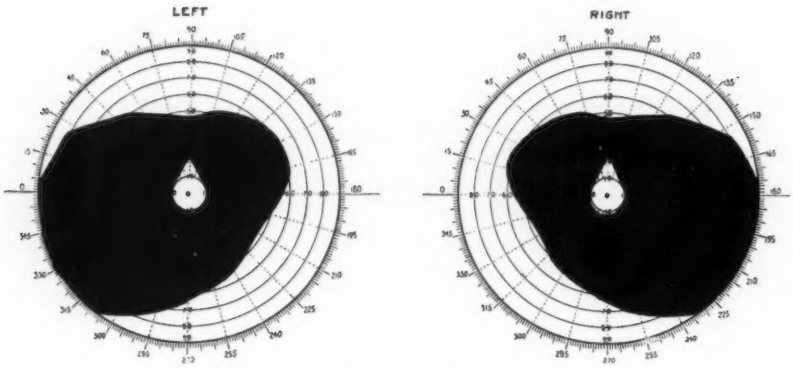

FIG. 8 (*Case* 1).—Perimeter.

The post-mortem examination by Dr. Carnegie Dickson revealed old-standing disease of the mitral valves, and on the auricular surface towards the centre of each cusp near the free margin an old medium-sized chronic vegetation. This was considered to be the origin of both the old and recent emboli responsible for the vascular lesions to be described. Both kidneys showed old, multiple infarcts. In the brain there was recent softening within the left middle cerebral territory with occlusion of the left internal carotid artery in its bony canal by recent thrombus extending into the middle cerebral artery. There was also a small unruptured aneurysm arising from the left internal carotid artery beneath the left optic nerve. On the under surface of the right cerebellar hemisphere there was a deep atrophic depression, presumably due to an old infarct. On the inner aspect of both occipital lobes there were deep, irregular areas of atrophy, evidently the result of some very old-standing vascular obstruction, giving a "shrivelled walnut" appearance in the brain in these regions, there being also a considerable atrophic depression on the under surface of the right occipital lobe towards its posterior pole (fig. 9, Plate LVI).

On horizontal section of the brain through the substance of the upper part of the arch of the corpus callosum marked atrophic shrivelling of the calcarine portion of the area striata was found on both sides, but particularly on the left, where on the inner aspect of the tip of the occipital pole and for a distance of some 4·0 cm. horizontally forwards on the medial aspect of the considerably dilated posterior horn there was a mingled mass of thickened, and probably to a large extent obstructed, arteries and atrophied cortex. At one part the brain tissue had completely disappeared and only some thickened vessels and leptomeninges intervened between the atrophic depression on the medial surface of the brain and the cavity of the tip of the posterior horn.

Case 2.—For the notes of this case we are indebted to Professor Witts, Dr. Bedford and Professor Daniel.

Mr. H., aged 69, was admitted to the Radcliffe Infirmary, Oxford, under Professor Witts on March 21, 1955. The history was obtained with difficulty as the patient was confused, but the main facts were as follows. For ten weeks he had been complaining of severe occipito-parietal headache. Two days before admission he complained of severe pain in his chest and collapsed. The next day he was confused and blind. On admission his only complaint was of his loss of vision. He was disoriented in space, asserting though he was in bed that he was in a garage, the location of which he gave. He gave the month and year correctly but was uncertain

of the date. He confabulated in the history of his illness, stating that he had lost his vision as the result of an accident. He said that he was standing in a yard with some of the lads and the vapours of an experiment exploded. All the others got out of the way but he lost his eyesight and had been unable to see much more than lights ever since. The examination notes on admission record that the fundi were normal and the pupils contracted normally to light. There was slight weakness of left face and arm. The tendon-jerks throughout were brisker on the left than the right. The left plantar response was extensor. There was no sensory loss. Absence of pulsation was noted in the anterior branch of the left temporal artery, and a biopsy later showed giant cell arteritis of this vessel. The erythrocyte sedimentation rate was at first 30 mm. and later 50 mm. in the first hour. He was treated with cortisone. Three weeks after admission it is reported that he was able to distinguish light from darkness and that the visual fields were very constricted to flashing lights. A week later he was seen by an ophthalmic surgeon, who thought it possible that the blindness was hysterical. At a later date he was able to appreciate gross movements in the left upper quadrants of the homonymous fields.

He was transferred to the Cowley Road Hospital under the care of Dr. P. D. Bedford on May 31, 1955, where it was noted two weeks later that he was alert, cheerful and co-operative and, except in a few small details, gave a very good account of himself. He was inclined to mix up the time-sequence of some events in his past life, but on the whole seemed well oriented and in touch with current events. His vocabulary was thought to indicate a high basic I.Q. but his performance on other tests suggested some mild recent deterioration. A note on his behaviour four days later reads as follows: "He locates a speaker quite accurately by turning his head to where he is. This gives the observer the impression that he is able to see. Continued observation leaves no doubt, however, that this is not so. His restlessness is due to a failure to accept this sudden and profound disability and is analogous to that seen in very old people after glaucoma operations. He crawls rather than walks for fear of tumbling over impediments. When he finds his chair again he identifies front from back, then left from right, and climbs up to sit in it." A further note on July 8, 1955, by a consultant in ophthalmology states that the patient at that time denied perception of light, though his other reactions suggested that his vision might be better than he would wish observers to believe. On July 27, 1955, there was a sudden onset of symptoms indicating a right cerebral lesion, and he died on the following day.

The post-mortem examination was performed by Professor Peter Daniel, the relevant findings being as follows. There were two old myocardial infarcts, one in the interventricular septum, the other in the anterior wall of the left ventricle, associated with diffuse atheroma of the coronary arteries. The left vertebral artery below the inferior cerebellar branch was occluded by firm thrombus. The right vertebral artery was yellowish and very thin. The upper extremity of the right internal carotid artery was occluded by white thrombus. The right posterior communicating was thread-like in size but looked normal. The brain showed a small, old infarct 1·5 cm. in diameter just anterior to the right precentral gyrus. There was cortical infarction of fairly long standing in both occipital regions, the cortex being yellowed over an area 4 cm. before back. It extended on to the inferior aspect of the lobe over an area 3 cm. in diameter and about the same area on the medial aspect. The calcarine cortex on both sides appeared to be involved (fig. 10, Plate LVI). There was cortical and subcortical softening of the left occipital cortex to a depth of about 1 cm.

Case 3.—Dr. Clifford Richardson, of Toronto, has kindly provided us with the notes of this case.

Mr. A., aged 58, was seen on December 7, 1948, the history being obtained from his son. Three months previously while at work he suddenly found that he could not

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see or understand the wiring he was trying to do. From this time onwards he had been confused and appeared to be totally blind. Dr. Richardson noted that he walked about with short, shuffling steps, groping as though blind, but found on testing his fields with a 5 mm. white object at 1 metre that he had a very constricted tubular vision on each side. At first he could see nothing on the Snellen's test chart, but was able after a while to distinguish occasional letters as low as 6/24. The fundi and pupillary reactions were normal and there were no abnormal signs in the nervous system apart from the visual defect. His blood pressure was 200/115. He was admitted on the same day to the Toronto General Hospital, where it was noted that there was almost complete blindness and severe loss of memory, but that in both respects there were outstanding discrepancies and bizarre inconsistencies. He would grope about, feeling his bed, asking if it was a bed. A short time later he would show indications of seeing much smaller objects on his bedside table or elsewhere in the ward. There was a general attitude of gross dependency and helplessness. He welcomed assistance by various other patients even more than the usual totally blind person would accept. Attempts to test his visual acuity gave varying responses, but he did at times see with 6/36 and 6/24 acuity. As before, it was possible to examine his visual fields with a fairly small white object. He showed a very small round, tubular field, extending only about 5 degrees from the centre point and remaining the same at different distances. These findings led to the conclusion that his amblyopia and dementia were both largely hysterical, and attempts were made at psychotherapy, with the aid of sodium amytal injections, without effect.

Eleven days after admission he suddenly became comatose with weakness in all four limbs and bilateral extensor plantar responses.

The post-mortem examination was made by Professor Linell. There was severe atheroma of the basilar artery, which was occluded throughout its whole length by recent thrombus. The pons showed extensive recent infarction. A small area (1·5 × 1 cm.) of old softening with cystic degeneration was present in the cortex of the left cerebellar hemisphere. The right occipital lobe was atrophied by comparison with the left and showed old cortical softening extending forwards for 2·5 cm. in front of the occipital pole to a depth of 3 cm. from the mesial aspect of the occipital lobe. Smaller areas of old softening with cystic degeneration were found in the subcortical white matter of the left occipital lobe in the distribution of the posterior cerebral artery, the largest of these areas measuring 1·5 × ·5 cm.

Case 4.—This case was briefly recorded by one of us (Symonds, 1948) and is here more fully reported by permission of *Revue Neurologique*.

R. W., aged 33, was admitted to the National Hospital, Queen Square, on March 17, 1947, under the care of Dr. Denis Williams, to whom we are indebted for leave to publish the case, with the complaint of failure of vision of acute onset. He had been in good health until November, 1944, when on the way to his work he felt dizzy and unable to walk. He was then admitted to hospital, where he was found to have a right hemiparesis with dysphasia. The cerebrospinal fluid contained a small number of red cells, but was otherwise normal. The Wassermann reaction was negative in blood and spinal fluid. He made a gradual, but almost complete, recovery from the hemiparesis but was left with some dysphasia. During the subsequent three years he had four generalized epileptic seizures. Six weeks before his present admission he began to have occipital headaches. These would occur several times a day, lasting for an hour or so. They were not associated with nausea or vomiting, but when severe were accompanied by visual disturbance, sometimes a momentary blurring of vision, and at others taking the form of coloured squares appearing before both eyes for several minutes at a time.

Ten days before his admission he woke with loss of vision in the lower half of both

fields, and blurring in the upper half, and within two hours became totally blind. On waking next morning he found he had recovered some vision in the upper fields. This state continued, with the occurrence of one further episode of total blindness up to the time of his admission. The intermittent occipital headache persisted throughout. On examination he was alert, conscious and co-operative. His speech was clearly enunciated but he would occasionally use a wrong word or phrase. Comprehension of conversation appeared normal. He was unable to read on account of his visual defect, and writing was severely handicapped for the same reason. He named common objects by touch. Visual acuity was limited to hand movements. The fundi were normal. The visual fields for a 20/2,000 white object showed a symmetrical central loss without peripheral constriction (fig. 11). The pupils were

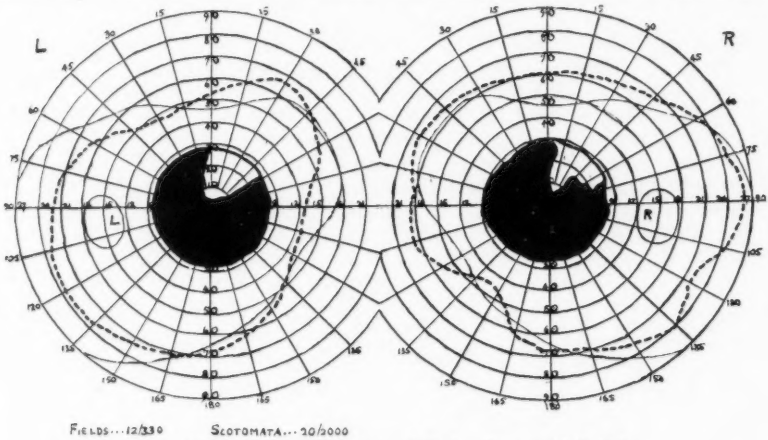

FIG. 11 (*Case* 4).—Perimeter 3/330. Screen 20/2,000.

dilated, but contracted normally to illumination, both direct and consensual. There was a slight weakness of the right face, and slight spastic weakness of the right limbs with increased tendon-jerks and an extensor plantar response on that side. There was no sensory loss. The blood pressure was 135/95. On March 20 he vomited and rapidly lapsed into a state of semi-coma. He was then found to have a quadriplegia, at first flaccid and later spastic, with the limbs extended, the fingers tightly flexed into the palm with thumbs adducted. Both plantar responses were extensor. It was subsequently noted that the corneal reflexes were diminished and that a fine, spontaneous, vertical nystagmus was present in the right eye. When the right lids were held open there was a slowly progressive downward deviation of the right eyeball, the left eye remaining in the normal position of rest. Later the right pupil became small and fixed, the left remaining dilated. He died in respiratory failure on March 22.

The post-mortem examination was performed by Dr. J. G. Greenfield. There was a large plaque of atheroma within the basilar artery, past which it was impossible to force fluid. The upper 1 cm. of the basilar artery was healthy, but there was a plaque of atheroma at its bifurcation. The posterior communicating arteries were small but quite free from atheroma. No atheroma was present in the internal carotid arteries or the left middle cerebral artery in the Sylvian fissure. The anterior communicating artery was likewise free from atheroma. The heart and aorta were healthy. There was a porencephalic defect about 4 cm. in diameter in the cortex of the anterior and

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superior opercula of the left island of Reil. In the pons there was extensive recent softening involving all the tissue on either side of the midline for about 1 cm. and extending dorsally to about 8 mm. from the floor of the fourth ventricle, and ventrally nearly to the surface. There was also softening along the lines of both calcarine fissures. The lesions in these areas when further examined were scattered hæmorrhagic softenings involving the posterior extremity of the calcarine fissure on each side, but with relative sparing of its lower lip on the left (fig. 12).

FIG. 12.—*Case* 4. Sections of the occipital lobes. The sections are marked R and L. They were numbered from behind forwards, and R 3 is thus the third section in front of the right occipital pole. The letter *C* indicates the calcarine fissure in each section. The black areas represent hæmorrhagic softenings. In the sections of the left occipital lobe the inferior lip of the calcarine fissure is relatively intact, corresponding with the sparing of the right upper quadrants shown in fig. 11.

Case 5.—Dr. Michael Ashby kindly brought this case to our notice and has allowed us to publish our observations.

W. C. R., aged 64, was seen by us on November 23, 1956. In his youth he had served in the Regular Army, subsequently became a policeman and then a transport driver, and had for eighteen years been a Trades Union official with a responsible position. He had no ill-health until November 1948, when he was admitted to hospital for a coronary infarction. There were further episodes of coronary infarction

in 1951 and 1953, but he was not left disabled and had carried on with his Trades Union duties up to the day of the illness now to be described. His own account of this is that on October 6, 1955, after breakfast suddenly something seemed to give way in his head. He remembers very little after this for the next four or five days. He has a vague recollection after the onset of being taken to his bedroom and shuffling along with his wife's help. He thinks he could see at that time, but later remembers seeing nothing except pitch black. Subsequently he had visions which he clearly remembers of flowers and papers hanging round him. He imagined himself at a cinema or theatre and remembers a box like a stand at an exhibition with various flags fastened to it and at the foot of each flag some acquaintance whom he knew to be dead. He thought he was to be the next. At the time he did not realize he was imagining things. In this period he knew people's voices but could not see them. The first thing he remembers seeing is his wife's face, only her face and not the rest of her. Next he could see some of the pattern on the carpet and the beading on his wardrobe. Of this he could gradually see more.

His wife's account was that after breakfast she left him about to go out to get his car, and on returning found him unconscious, sprawled across the table. She got him into an armchair, and he vomited. He continued to vomit and remained unresponsive until 4 p.m. He then came to himself and said he wanted to go to bed. When he got up he was able to walk but could not find the door and asked to be led. That night he did not take much notice. Next morning she gave him a cup of tea and he said "Nance, I can't see it. Everything is black." During the following six days he remained blind and was confused and disoriented at night time. On the seventh day he could see part of his wife's face or a cup of tea but could not see well enough to take it from her or feed himself. A month after the onset he got out of bed and moved about the room, but his wife had to lead him. At this time when given a bowl of water to wash his hands he would fumble and fail to put his hand in it. Since than he has gradually improved.

On examination he was a healthy-looking man, alert, cheerful and vigorous, giving his history well and showing no defect of memory or attention. He talked clearly about subjects in which he was interested and showed good judgment. There was no evidence of dysphasia. Hearing was normal. Visual acuity was 6/5 in each eye. The fundi were normal with only a little nipping of the veins by the arteries. The visual fields, examined on the Bjerrum screen, were, as shown, restricted to an area which nowhere extended as far as 10 degrees from the fixation point (fig. 13). The pupils

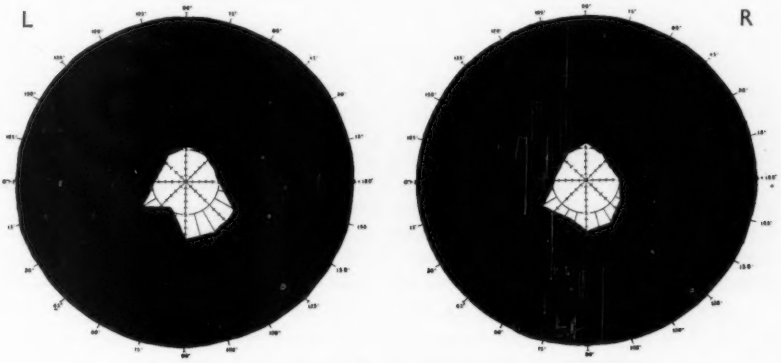

FIG. 13 (*Case* 5).—Screen 2/2,000, 15/2,000 and 30/2,000.

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were of medium size, regular and central, contracting to light through a small range and perhaps more slowly than normal. The only abnormality of cranial nerve function detected was depression of the right corneal reflex.

There was no weakness or dystonia, but a slight ataxia in the performance of the right heel-knee test. All the deep reflexes were present and equal, and both plantar responses flexor. There was no loss of sensation to pin-prick. The sense of passive movement was normal in the toes, and two-point discrimination accurate at 6 mm. on the fingers. His gait was normal, but to steer a course he depended upon his wife's guidance. The blood pressure was 150/98: the heart sounds were distant.

Case 6.—W. E. P., a retired engineer aged 75, was first seen by one of us (C. P. S.) on December 3, 1936. He had had no previous illness and had been driving his car on the day before the ictus. He was found when called in the morning to be confused and complaining that he was blind. He was seen by a doctor, who observed that his pupils contracted to light, and a nurse was installed, who observed that at that time he did not know who or where he was and had no vision at all. No disturbance of speech function was observed nor any weakness of the limbs. When examined five weeks after the onset he stated that some vision had returned. He was a little confused but able to co-operate for perimetry, which revealed integrity of the left inferior quadrants of the visual fields with complete loss of the remainder. Macular vision was preserved in the intact quadrants only.

When examined two months later he was quite clear in his mind. He did not think his vision had improved, and to confrontation the visual fields appeared as before. A large red object was nowhere truly appreciated. The best that he could give was yellow or dirty red in the centre. He was able to read with great difficulty. This, as he had appreciated for himself, was due to his inability to pick up more than a few letters at a time. He was able to see to get about, but complained of difficulty in recognizing even familiar surroundings, and of visual hallucinations—curtains of various colours blowing in the wind, also people and animals, mostly dogs of a mongrel type. These he had taught himself to disregard.

Two months later his condition was unchanged. The impairment of colour vision was confirmed. Red was appreciated as reddish or rosy in the centre, green not at all, blue correctly. A month later he was the same, and the visual fields on the perimeter were as when he was first seen. Three months later he suddenly felt giddy and complained of headache. This was immediately followed by "horrible" visual hallucinations. The whole of the wall and floor seemed to be covered with caterpillars in serried ranks—not moving. This continued for several hours. Then his surroundings seemed to be dilapidated—broken walls and pipes, and furniture broken. During this phase his vision became worse. He also noticed weakness of the legs, the left more than the right. Since the recent episode he had found himself quite unable to visualize anything—for example, his house or garden, or people. He had been a keen motorist and now found that he could not visualize a road or route, which deprived him of all interest in being driven.

His visual fields were not charted on this occasion, but confrontation tests showed a notch gone out of the upper part of the left inferior quadrants.

He was seen for the last time four months later, when his condition was unchanged except that the visual hallucinations had ceased. He complained, however, of seeing objects moving at times when he knew they were not.

Case 7.—Mrs. G., aged 74, was seen by one of us (C. P. S.) in 1938. She was known to have had rheumatic heart disease for many years but otherwise well until one year before the present illness she had an attack in which she suddenly lost vision partially, was giddy and recovered in an hour or so. Six months later she had another

attack and on this occasion was for some hours unable to see anything to the left. From this she recovered though she thought since then her vision had possibly been less accurate. Four days before the date of examination in the evening she suddenly became completely blind, unable to distinguish light from darkness. There was no headache before or at the onset, and both at that time and afterwards she remained clear in her mind. The doctor who saw her shortly after the onset found her pupils contracting normally to light.

On the day before the examination she was for the first time able to tell when the electric light was turned on and off. She proved to be alert but a little uncertain of her orientation in time and not a good witness. The fundi were normal. Examination of the visual fields with an electric torch showed a single area about the middle of the left inferior quadrants where she recognized the light and pointed to it accurately. She denied any visual hallucinations or loss of visual imagery. Both pupils were moderately dilated, and contracted promptly and through a normal range to light, and on convergence. Apart from the loss of vision there were no abnormal signs to be found in the examination of the nervous system. The blood pressure was 215/110 and the heart much enlarged, with mitral and aortic regurgitation.

Case 8.—Mrs. C., aged 70, was seen by one of us (C. P. S.) in 1950. She was said to have had no previous illness except that she was reported to have been seen by a consulting physician on account of heart trouble eleven years previously. Two months previously she had had a sudden attack of vertigo with vomiting. These symptoms continued throughout the rest of the day and the following night, and when she awoke on the following morning she said that she could not see. She was confused and disoriented. Her mental state had improved, and she was able to be up and about and was brought to the consulting-room. As far as her relations could judge she remained completely blind. On examination she proved to be a well-preserved and well-mannered old lady, but confused and disoriented and with a defective memory for recent events. The fundi were normal and the pupils contracted normally to light. Vision was tested by switching on and off an electric torch. It was clear that she had some preservation of central vision, probably better on the left than the right. Within these limits she was able to say "on" and "off" correctly when the torch was operated, but when asked to touch the torch her hand groped in any direction, only occasionally, and by chance, the right one. There was no dysphasia, nor any other abnormal physical signs in the nervous system.

Further examination three weeks later confirmed the previous observation. She was seen again a month later, when her relations reported her mental state clear and her vision improved. She was said to be able to discuss business affairs and write letters and had been to a garden party before the consultation. Her behaviour was still that of a person who was practically blind. She was said, however, to be able to read large print. She had difficulty in distinguishing between figure and background. She would think a person part of a wall, or confuse the lower part of a person with the pattern of the carpet. Examination of the visual fields by confrontation showed that she could now see a good deal in her lower fields, the right better than the left, but nothing in the upper halves. She could distinguish a large red test object from a white in her right lower quadrants. She could also trace with her finger outlines of the largest letters of the Jaeger test type and describe their shape—for example, a half circle facing to the right for C, but was unable to identify the letters. She was quite unable to judge the position of objects in relation to one another or herself. She died suddenly five months later. There was no autopsy.

Case 9.—S. S., a retired civil servant aged 72, was referred to one of us (C. P. S.) by Dr. Robert Lansdown, who supplied valuable information, on April 9, 1955. In June 1953 he had a coronary thrombosis, confirmed by an electrocardiogram, with

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satisfactory recovery, though he was left with occasional angina of effort. One month before he was seen he stood up after reading the paper and found his right arm heavy, without any numbness or tingling. This was in the afternoon, and next day he found that he was unable to write or strike a chord on the piano. At the same time he noticed some difficulty in reading. He found when he got to the end of a line in a newspaper he would transgress the column, continuing on the same line instead of beginning the next. The reading difficulty disappeared in the course of the next day or two, and the use of his right hand returned, but was imperfect, being a little clumsy.

Twelve days later he noticed in bed that one of his legs was weak, he could not be sure which, but on getting out of bed next morning he collapsed and then found that his left leg dragged when walking. This rapidly improved, but three days later he suddenly noticed that his left arm was heavy. Again there was rapid improvement, but a few days before his visit he found his right leg a little awkward. His present complaint, in his own words, was lack of co-ordination in all his limbs. He was a well preserved, intelligent man, whose chief concern was lest he should become a helpless invalid and a burden upon old friends with whom he was living in his retirement.

On examination there was no dysphasia. The fundi were normal and the visual fields full to confrontation. There was no cranial nerve defect. Extension of the left wrist and fingers was perhaps slightly weaker than it should be, but the piano-playing exercise was equally well executed with both hands. The tendon-jerks were all present and equal on the two sides. The left plantar response, though flexor, was not so easily elicited as on the right. There was no sensory impairment. There was therefore remarkably little to show for his complaint, but in view of the quadriplegic distribution of his symptoms and his own conviction that the motor function of all four limbs was impaired, the diagnosis of stenosis of the basilar artery was made.

On April 29, 1955, he was admitted to Guy's Hospital under the care of Dr. M. J. McArdle, with whom he was seen again. The only abnormalities then found on neurological examination were a slight falling away of the outstretched right arm with minimal generalized weakness of this limb: an extensor plantar response on the right and an occasional extensor response on the left. He was at that time quite clear in his mind, and routine tests of intellectual function revealed no impairment of memory, or learning ability.

He was readmitted on January 2, 1956. The history since his discharge was that early in August 1955 there had been a sudden onset of weakness in the right arm and left leg with gradual recovery in the course of three or four weeks. On September 10 he suddenly became confused. He declared that his body was dead, but his head was alive. He would pull up the plants in the garden and say they had no roots. He also complained of "seeing things that were not there"—for example, non-existent traffic in the road, birds flying down, people coming out of gates and a cat climbing up a tree. A week later he was admitted as a voluntary patient to a mental hospital, where he was recorded as being confused and agitated with nihilistic delusions and visual hallucinations. The diagnosis made was arteriosclerotic dementia. He was discharged at the end of two months having recovered.

A month before his second admission to Guy's he suddenly complained of impaired vision, which had not improved. A week later he began to have recurrent attacks of paroxysmal vertigo with vomiting and headache and intermittent faintness. These symptoms had subsided by the time of admission. Examination on this occasion revealed impairment of recent memory but no other mental abnormality. Hearing was normal. The visual acuity was J.16 right and J.10 left. The fundi were normal. The visual fields on the Bjerrum screen showed homonymous defects, including loss

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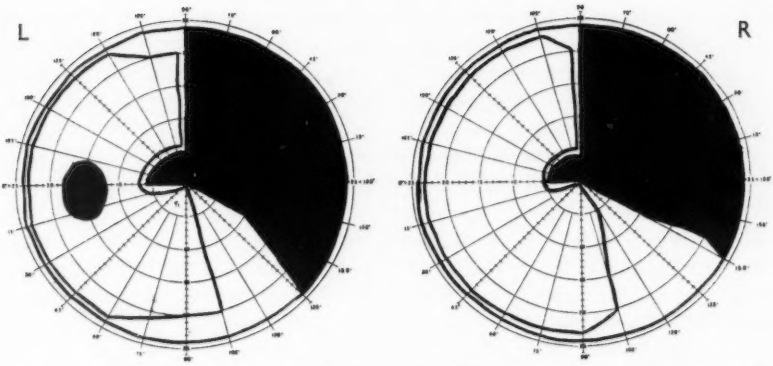

FIG. 14 (*Case* 9).—Screen 3/2,000 and 15/2,000. On the perimeter the right homonymous defect extended to the periphery, the remainder of the peripheral fields being intact.

of the right superior quadrants and part of the inferior quadrants, and a central scotoma in the left upper quadrants (fig. 14). Both corneal reflexes were diminished. The tongue was protruded slightly to the right. All the limbs were a little spastic with slight weakness of shoulder abduction, and elbow and wrist extension, in the right arm, and of hip flexion in both legs. Co-ordination was normal. All the tendon-jerks were abnormally brisk, the right arm-jerks more than the others. The plantar responses were flexor. Sensation to touch and pin-prick was normal. There was no loss of postural sense in the fingers or toes, and two-point discrimination in the fingers was accurate at 0·5 cm. He was discharged after three weeks unchanged, his only complaint being that of defective vision. A fortnight later he was found in the morning comatose. Dr. Lansdown was called and found him with a flaccid quadriplegia, and he died a few hours later. Leave for a post-mortem examination was not granted.

DISCUSSION

General clinical data.—Of the 58 patients 48 (83 per cent) were males, and of 54 patients whose age was recorded 41 (75 per cent) were over the age of 50. These figures agree very nearly with those for cardiac infarction.

5 patients of the series had a previous history of coronary thrombosis, 4 had rheumatic valvular disease and 2 cardiac arrhythmia (both probably auricular fibrillation). 3 at some time before the onset of visual loss had had a cerebral vascular lesion resulting in hemiplegia.

Prodromal symptoms were recorded in less than half the cases in which details are available. The commonest were transient episodes of visual impairment, and vertigo. In 5 cases the syndrome of basilar stenosis (Denny-Brown, 1953; Silversides, 1954) was recognizable for some time before the onset of visual loss. Our Case 9 provides an example.

The loss of vision was of sudden onset in 47 cases and gradual in 5, the mode of onset in the other 6 cases being uncertain. The right and

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left half-fields were involved simultaneously in 42 and successively in 12 of the cases in which details are available. Thus the common mode of onset appears to have been a sudden loss of both half-fields, but in several instances there had been complaint of visual deterioration before the episode of sudden loss.

Loss of consciousness at the onset occurred in 10 cases.

Headache occurring shortly before, or with, the loss of vision was a prominent symptom in 11 cases, and vertigo is mentioned in 10.

The onset was accompanied by confusion in 25 of the 50 cases in which the history is available. It appears that there is less likely to be confusion if the onset is gradual, and if the two half-fields are successively, not simultaneously, involved.

The visual defects observed.—Of the 58 patients in this series 14 remained totally blind, but in 4 instances death occurred within three months of the onset, making it uncertain whether some vision might not have returned. When at the time of examination there is complete blindness with no perception of light, the association of this with normal fundi, or at least fundi in which no reason can be found for loss of vision, together with normal pupillary reactions to light, may arouse the suspicion of hysteria, as it did in our Case 2. Under these circumstances, as Magitot and Hartmann (1926) have emphasized, the only objective evidence of organic blindness is loss of reflex blinking to menace. Although recorded by Lagrange, Bertrand and Garcin (1929) and by Hemphill (1941) in his second case, this important sign seems generally to have been neglected.

In the 44 cases in which there was some sparing or recovery of vision the visual fields showed considerable variation, but with a significant recurrence of certain patterns. Thus in 27 cases there was some preservation or return of central vision. In 11 of these the area preserved was in the form of a circle around the fixation point, extending to about 10 degrees, as illustrated in our Cases 1 and 5 (figs. 8 and 13). In 10 cases the area preserved was central but less than circular. In the 2 cases of Marie and Léri there were no perimetric observations, but there was probably central vision restricted to the right half-fields. The cases of Raymond and others (1906), Bramwell and others (1915) and Reese (1954) provide examples of the same semilunar pattern verified by perimetry. Preservation of central vision limited to a single quadrant was recorded by Riley and others (1943) and by Reese (1954). Preservation of a semilunar area below the horizontal meridian (Förster, 1890) and above it (Knies, 1896; Kearns, Wagener and Millikan, 1955) have also been observed (fig 7).

The patient with preservation of central vision alone, even though this extends only a few degrees from the fixation point, will have good, or relatively good, visual acuity in both eyes, although his behaviour resembles that of a blind person. This apparent incongruity was perfectly

described and explained by Förster (1890). The observation of Jacqueau (1900) that his patient could see the head of a glass pin but everything around it was black, and the ability of Bramwell's patient (1915) to pick up a pin from the floor while preserving only a few degrees of central vision in the right half-fields provide other examples. Yet, as Terrien (1938) observed, the patient in this condition is unable to get about owing to the restriction of the fields. He may also fail to recognize large objects, even if they are familiar, for he cannot see them as a whole. This disability was well described in our Case 5, as having been present in the earlier stage, and when we examined the patient we observed a man of a clear, independent and vigorous mind, who was much dependent upon his wife for help whether in the house or in the streets, despite a visual acuity of 6/5 in each eye. Discrepancies of this kind had led to the suspicion of hysteria in our Cases 1 and 3.

In 6 cases there was preservation of an area of central vision together with a sector or sectors extending from this central area towards the periphery. In each instance the sectors preserved have been adjacent to the vertical meridian (Allyn, 1896 (fig. 3); Kustermann, 1897 [Case 2] (fig. 4); Holmes, 1934; McDonald, 1943 (fig. 5); Ross, 1949 (fig. 6); Kearns, Wagener and Millikan, 1955 (fig. 1)).

In some cases initial blindness has been followed by full recovery of vision in one-half or one-quarter of the fields. In three instances the patient has been left with a hemianopia (Biemond, 1951; Jacqueau, 1900; Reese, 1954). In our Case 6 there was preservation of the left inferior quadrants only. In Kustermann's Case 1 there was peripheral sparing of the left upper quadrants, and in 4 other cases there has been ill-defined quadrantic sparing for light and darkness or hand movements (Dejerine and Vialet, 1893; Hemphill, 1941, and our Cases 2 and 7). In our Case 8 there was some return of vision in the lower fields of both sides, but the patient could not co-operate for perimetry. Lack of co-operation has prevented any estimate of the part of the field in which vision was preserved in 3 of the recorded cases in which the loss was incomplete as judged by tests of light or darkness or hand movements.

We are left with 4 cases in which there was central loss with some degree of peripheral sparing or recovery. In one of these (Lawrence, 1952) the evidence is only that vision was reduced to light perception peripherally. The others are our Cases 4 and 9 and the case of Groenouw (1892) (figs 11, 14 and 2).

Psychological disorder.—Confusion at the onset has already been mentioned as occurring in half the cases. Spatial disorientation in the absence of confusion has been a prominent symptom in some of the recorded cases and is described in some detail by Groenouw (1892). When present it adds greatly to the disability due to visual loss, but it is

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clear that loss of vision may occur from occipital lobe infarction without this symptom and that the same is true of visual agnosia, loss of visual imagery and loss of colour vision. Any of these symptoms may be present, but they are inconstant. In our Case 6 loss of visual imagery was not present after the original lesion, but followed a second which caused only a slight increase of the visual defect.

Magitot and Hartmann (1926) in their excellent review of the subject conclude that the calcarine cortex serves primitive vision and that the elaboration of visual percepts is a function of the neighbouring cortex, especially that of the occipital lobes. One may, therefore, observe as the result of circumscribed lesions in this region blindness without perceptual disorder, or the reverse, and in some cases a combination of both.

Visual hallucinations appear to be a relatively uncommon feature of the syndrome. They were a persistent symptom in the case of Lagrange, Bertrand and Garcin (1929) and occurred during the confusional state after the ictus in our Case 5. They were also described in a state of clear consciousness in our Case 6, being suddenly increased after a second lesion, causing slight increase of the visual defect. Of special interest is the acute hallucinatory psychosis in our Case 9, which began and ended some time before the lesion which caused visual loss. Assuming that the visual hallucinations were due to a vascular lesion, we may argue that its site was not the same as that responsible for the subsequent loss of vision. We may conclude, therefore, that although any of the above symptoms may result from bilateral occipital lobe infarction causing visual loss, they are not dependent on the lesions of the visual cortex or radiations responsible for the loss of vision.

Denial of blindness has been given a prominent place among the symptoms of so-called cortical blindness and has by some authorities (Magitot and Hartmann, 1926) been regarded as distinctive, never occurring with blindness from a peripheral cause. This symptom is well described in 2 cases of total blindness (Dejerine and Vialet, 1893; Lagrange, Bertrand and Garcin, 1929) and less certainly in two others (von Monakow, 1885; Kearns, Wagener and Millikan, 1955). But this variety of anosognosia is certainly observed in patients with loss of vision from disease of the retina and optic nerve (Redlich and Dorsey, 1945). We must conclude, therefore, that it is not pathognomonic for blindness from occipital lobe infarction, but is more likely to occur in blindness from this than from other causes for two reasons. Some of these patients suffer from agnosia involving a neglect of extra-personal space, which as Sandifer (1946) has argued predisposes towards anosognosia for blindness, and in many of them there is intellectual deterioration with impaired judgment.

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The Anatomical Basis of the Visual Field Defects

The representation of visual function in the occipital cortex is well established, largely due to the work of Holmes (1918), Holmes and Lister (1916), Holmes (1931, 1934) and Spalding (1952*b*). The last named writer has concluded from the data afforded by small gunshot wounds that central vision within the 8 degrees to 10 degrees circumference is represented on that part of the striate cortex which faces posteriorly or postero-medially, i.e. at the posterior termination of the calcarine fissure. It appears also that the horizontal meridian of the visual field is represented in the floor of the calcarine fissure, and the neighbouring sectors above and below this in an order such that the vertical sectors are projected on to those parts of the striate cortex farthest removed from the fissure. This is beautifully illustrated by the case of bilateral occipital softening reported by Holmes (1934). Having regard to these observations we can readily visualize the areas of cortex which must have been spared to account for the sparing of the visual fields, provided that we consider the problem in relation to the cortex only. It must, however, be remembered that softenings of the extent that have been recorded may well have involved the optic radiations, as was shown in the case reported by Dejerine (1901) in which, despite an almost complete blindness, a considerable area of the visual cortex was intact. If for the moment we consider the visual fields recorded in these cases in terms of presumed cortical damage the following conclusions may be drawn. The area of vision most commonly preserved is a circle extending to about 10 degrees from the fixation point, corresponding with the area of cortex referred to above (Spalding, 1952*b*). In an almost equal number of cases the area of vision preserved is central but semilunar or quadrantic, corresponding with a smaller lesion within this area of cortex. In 4 cases in addition to central circular sparing there was preservation of vision in a sector or sectors adjacent to the vertical meridian, corresponding with those parts of the striate cortex farthest removed from the calcarine fissure. These cases together constitute 25 of the 44 in which some vision was preserved, and we may add to these as examples of sparing of the vertical sectors the cases of Holmes (1934) and Kearns, Wagener and Millikan (1955). It would seem, therefore, that, when there is infarction of the medial aspect of the occipital lobes, the cortex at the posterior extremity of the calcarine cortex is least vulnerable, and that the visual cortex at a distance from the calcarine fissure is less vulnerable than that within it. We have at the same time to note in one of our own cases selective loss of central vision, indicating destruction limited to the cortex at the posterior extremities of the calcarine fissures.

The arrangement of the fibres of the optic radiation in relation to the parts of the visual field which they serve is less precisely defined. The evidence on this matter has been reviewed by Spalding (1952*a*), who has added observations of his own on the visual field defects resulting from

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gunshot wounds involving the radiation at different levels, both in the vertical and antero-posterior planes. He has postulated with good reason that in its posterior part the radiation has in coronal section the form of a horseshoe, which embraces the posterior horn of the lateral ventricle with its open end towards the medial surface of the occipital lobe. From the two ends of this horseshoe the fibres of the radiation pass to the striate cortex above and below an imaginary line running lengthwise through the centre of the calcarine fissure. The fibres serving central vision lie in the centre or bend of the horseshoe, as seen in coronal section, lateral to the posterior horn of the ventricle. The arrangement of the fibres within the intermediate and anterior parts of the radiation we need not discuss in this paper, which is primarily concerned with lesions of the occipital lobes. It must, however, be remembered that blindness or near-blindness can result from bilateral lesions of the optic radiations in any part of their course, though when the cause is infarction, damage to the anterior part of the radiations, that is to say in front of the occipital lobes, is likely to cause symptoms and signs additional to visual loss, unless the areas of softening are exceptionally small. Hemianopia, however, may be the most evident symptom when the radiation is involved in front of the occipital lobe as in a case reported by Man and Gruner (1952). Although at the onset their patient had a left hemiparesis, the outstanding symptom was visual loss, at first complete blindness, with some return of vision in the left upper quadrants of the fields. Post-mortem examination showed occlusion of the left calcarine artery with destruction of the visual cortex, and, on the right, occlusion of the terminal part of the middle cerebral artery with softening involving the optic radiation, the right occipital lobe being intact.

The preservation or recovery of central vision in cases of softening involving the optic radiations is not easily explained. Lagrange, Bertrand and Garcin (1929) regard this as a relatively frequent occurrence, arguing that the presence of complete blindness as opposed to macular sparing is in favour of lesions of the visual cortex as opposed to lesions of the radiations. The evidence accumulated in the present paper appears to contravene this assumption. Foix and Schiff-Wertheimer (1925) however, record the case of a man admitted to hospital with a right hemiparesis, dysphasia and severe visual impairment, in whom perimetry showed preservation of vision only in a roughly circular area extending 10 degrees to 15 degrees from the fixation points. The post-mortem examination showed several areas of softening in the left hemisphere, one of which extended from the external surface of the occipital lobe, well in front of its pole, in the shape of a wedge whose apex had cut into the optic radiation. There was a single comparable area of softening in the right hemisphere situated more anteriorly. For the escape of central vision in this case we can offer no explanation. It might on the other hand be possible to explain the escape

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of central vision when the optic radiations are involved in the posterior part of their course in a zone of infarction based upon the mesial surface of the brain, supposing that this did not extend deeply enough to destroy the centre of the horseshoe as represented in Spalding's diagram (1952*a*).

It is evident that infarction of the occipital lobes, whether or not the visual cortex is involved, must often damage the optic radiations. The case of Dejerine (1901) provides an important example. Vialet (1893) also draws attention to this point. It seems probable that this is the explanation of the case reported by Bramwell, Bolton and Robinson (1915), in which there was sparing of a few degrees of central vision in the right half-fields. The striate cortex was reported as histologically normal except at its right posterior extremity, and it is also stated that the optic radiations were intact. But no microscopic evidence is provided in support of the latter statement, and from the extent of the softening shown in the photographs it seems likely that the optic radiations were involved.

The well-defined quadrantic sparing of the fields observed in our Case 6 was an unusual feature. Its anatomical basis may perhaps be deduced from the observation of Beevor and Collier (1904). In this case a well-defined left upper quadrantic loss was correlated with an area of softening on the mesial aspect of the right occipital lobe situated almost entirely below the calcarine fissure. Serial sections of the occipital lobe in the coronal plane showed that the softening extended deeply to involve the mesial wall of the posterior horn of the lateral ventricle in its lower half and extended in this position as far forwards as the splenium of the corpus callosum and backwards to the posterior extremity of the calcarine fissure. The terminal fibres of the optic radiation destined for the lower half of the visual cortex must therefore have been destroyed. It is probable that in our Case 6 the lesion responsible for the left upper quadrantic loss occupied the same situation.

The Arterial Blood Supply to the Visual Cortex and Optic Radiations

The visual cortex is supplied by the twigs of the calcarine branch of the posterior cerebral artery. The limits of distribution of this branch according to Shellshear (1927) coincide almost exactly with the striate cortex both on the mesial and lateral surfaces of the hemisphere. Abbie (1938), however, states that the peripheral fringe of the striate cortex, as it appears on the lateral surface of the brain, is supplied by anastomosing twigs from the middle cerebral artery.

Beevor (1909) in the course of his exhaustive experiments with injections of coloured material into the cerebral arteries found that the demarcation between the distribution of the posterior and middle cerebral arteries varied in its position from brain to brain. The area of most common distribution of the middle cerebral artery is shown in his diagrams to fall

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short of the occipital pole by ¼ to ½ an inch, and in some brains was much farther removed from it. He observed, however, that the communication between the superficial branches of the different arteries was so free that it was possible to inject the area of the posterior cerebral artery through the middle cerebral artery or vice versa, the posterior communicating artery being ligatured. His observations on this point are convincing and relevant to the preservation or restoration of central vision after infarction. He states "This communication between the areas of two different arteries is well shown by the following observation which I have repeated several times. If the anterior, middle, and posterior cerebral arteries be injected with three different colours and with the same pressure, until there is a well marked demarcation—let us say—between the middle and posterior cerebral areas, and if now the tube supplying the middle cerebral artery be clamped, it will be seen that the injection for the posterior cerebral area will invade that of the middle cerebral area and drive its colour out, but on releasing the clamp on the middle cerebral artery tube, the invading injection from the posterior cerebral area will be driven back until the original border line is attained." Vander Eecken and Adams (1953) have recently confirmed the existence of such anastomoses and emphasized their importance in determining the extent of infarction following embolism or thrombosis.

Beevor (1909) also investigated the blood supply to the optic radiations, and found that the anterior part of the radiation was supplied by the anterior choroidal artery. Abbie (1938) found this vessel to supply only that part of the radiation in which the fibres pass laterally to gain the lateral aspect of the descending horn of the ventricle, the radiation behind this point, and as far as the termination of the posterior horn of the ventricle, being supplied by the deep optic branch of the middle cerebral artery, which enters the brain through the anterior perforated substance with the lateral striate arteries. In either case the blood supply is from the middle cerebral artery. Beevor (1909) concluded that the posterior part of the radiation derives its arterial supply as follows. In front of a coronal section through the anterior end of the calcarine fissure the upper three-fourths of the radiation are supplied by the middle cerebral artery while the inferior one-fourth is supplied by the posterior cerebral artery. Behind this plane the upper fibres of the radiation continue to lie within the middle cerebral territory until within an inch of their termination, from which point the whole of the optic radiation is as a rule supplied by the posterior cerebral artery. He found, however, that "after ligaturing the occipital artery of the posterior cerebral just anterior to the internal parieto-occipital fissure" injection from the middle cerebral readily injected all the posterior cerebral area, including the optic radiations. He concluded that the softening produced in pathological cases must be "due to a rapid extension of the thrombus into the minute arterioles or else to

embolism of the fine arteries, for it is not possible to cut off the blood supply to the cuneus and gyrus lingualis by simply ligaturing the occipital artery as the circulation to the posterior cerebral area can be so readily restored through the branches of the middle cerebral artery."

One further observation made by Beevor (1909) is pertinent. He could find no evidence of anastomosis between "the fine arteries of the cortex" after they had penetrated the brain substance. "If the pia mater be carefully stripped off, or a circular incision be made through the pia mater, that part of the cortex denuded of membrane, or the part inside the circle, will not be injected, and will not receive any blood from the small cortical arterioles in the brain substance surrounding this area."

Pathogenesis.—It has been argued by some of the authorities that have been quoted that in all cases in which bilateral loss of vision results from occipital lobe infarction there has been a previous unnoticed hemianopia, but the clinical history in many cases, and the not infrequent post-mortem finding of infarctions apparently of the same age on the two sides, are opposed to this assumption. Therefore, whatever may be the pathogenesis of this condition it must allow for the possibility of simultaneous infarction of both occipital lobes in a large proportion of the cases. The simplest explanation of this would be embolism arising from a source proximal to the bifurcation of the basilar artery. In 8 of the cases we have reviewed or presented there was a potential source of embolism in the shape of a recent coronary thrombosis, mitral disease or auricular fibrillation, and in 3 others there was a previous history of coronary thrombosis. In such cases it is reasonable to suppose that, an embolus having lodged at the bifurcation of the basilar artery, fragments were shed which were more or less symmetrically distributed between the two posterior cerebral arteries. Three of this group of cases came to post-mortem examination, and the findings were consistent with this hypothesis.

Among the other cases with proved bilateral occipital lobe infarction, 30 in number, there is an adequate description of the basal arteries in only 10, this observation being often neglected. In 7 of these the basilar artery was occluded by thrombus. In one case (Holmes, 1934) there was extreme narrowing of the basilar and almost complete occlusion of the left internal carotid arteries by atheroma, and in another (Berger, 1885) occlusion of the right internal carotid and left posterior cerebral arteries. In one case (Riley *et al.*, 1943, Case 4) there was occlusive thrombosis of the left vertebral and posterior cerebral arteries, the right vertebral artery being congenitally small.

It is evident, therefore, that stenosis of the vertebrobasilar system, expecially if associated with occlusive thrombosis of the basilar trunk, plays an important part in determining bilateral occipital lobe infarction.

It might at first be supposed that obstruction of the basilar artery would account for the infarction of the occipital lobes as the result of a

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diminution of the flow through the posterior cerebral arteries. This, it might be assumed, would be most sluggish in their distal branches, in which thrombosis would be therefore most likely to occur. There are reasons, however, against this hypothesis. Pathological examination in cases of basilar occlusion with pontine infarction reveals infarction of the occipital lobes in only a minority of cases. Thus Kubik and Adams (1946) recorded 17 cases in which the basilar artery in some part of its length was occluded by clot. There was infarction of the pons in all cases, but of the occipital lobes in only 7, and in only one of these was the occipital lobe infarction bilateral. In the 7 cases of their series in which the basilar thrombosis extended distally into both posterior cerebral arteries occipital lobe infarction was present bilaterally in 1, unilaterally in 4 and absent in 2. In one case in which the thrombus extended along both posterior cerebral arteries far enough to block the junctions with both posterior communicating arteries there was infarction of the left occipital lobe only.

The survival of both occipital lobes in certain cases after occlusion of both posterior cerebral arteries at their origin, and of one occipital lobe when the posterior communicating artery on that side was also occluded, is in accord with Beevor's observation quoted above that the posterior cerebral territory can be filled by injection of the middle cerebral artery after ligation both of the posterior cerebral and posterior communicating arteries. Some other factor, therefore, must be invoked if we are to explain in terms of diminished blood flow the *inconstant* association of occipital lobe infarction with basilar occlusion. This factor may be an associated stenosis of one or both internal carotid arteries, such as was present in the cases of Berger (1885), Holmes (1934) and in our Cases 1 and 2. Hutchinson and Yates (1956) have emphasized the frequency and importance of this association, and it is now well recognized that the common site of internal carotid stenosis is in the neck. This was not fully appreciated at the time of the paper by Kubik and Adams (1946) so that the existence of internal carotid stenosis might have been missed in some of their cases.

Hutchinson and Yates (1957) have further emphasized the importance of examining the vertebral arteries in the neck, pointing out that occlusion or narrowing in this part of their course may be an important factor in causing cerebral infarction, and may sometimes exist when there is little evidence of disease in the intracranial arteries. One of their cases is especially relevant to the present discussion. Their patient, having had preliminary symptoms of brain-stem ischæmia, died with the signs of pontine infarction and at autopsy in addition to this, and infarcts in both cerebellar lobes, there was bilateral infarction of the occipital lobes. The carotid arteries throughout their course were normal as also were the intracranial arteries generally, but the right vertebral artery was occluded by organized thrombus extending from its point of entry into the vertebral

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canal opposite the sixth cervical vertebra to the level of the atlas. The left vertebral artery was half the size of the right and "partially stenosed by atheroma." With this case we may compare that already mentioned (Riley and others, 1943) in which blindness from occipital lobe infarction was associated with thrombosis of one vertebral artery and congenital smallness of the other. Hutchinson and Yates attribute the occipital lobe infarctions in their case to the diminished blood supply, but against this explanation must be set the observations and conclusions that we have already presented.

We believe it more probable that in most, if not all, cases in which there is vertebral or basilar thrombosis the infarction of the occipital lobes results from emboli derived from the clot. Fine emboli plugging the penetrating branches of the calcarine artery at its termination will cause infarction of the occipital poles with consequent loss of central vision as in Groenouw's case and in our Cases 4 and 9. Larger emboli lodging more proximally in the calcarine artery will cause infarction of the cuneus and lingual gyrus, but the deep penetrating branches at the posterior extremity of the visual cortex will have their blood supply preserved by the anastomosis between the superficial branches of the posterior and middle cerebral arteries in this area. Furthermore, when the calcarine artery is occluded the cortex supplied by its short penetrating branches is more likely to suffer destruction than that supplied by the longer branches which have opportunity for anastomosis before leaving the surface. Hence those parts of the visual cortex farthest removed from the depths of the fissure have a greater chance of survival, and after the area of central vision the sectors adjacent to the vertical meridian are most likely to be spared.

In support of the embolic hypothesis an analogy may be found in the sequence of events following compression of the subclavian artery by a cervical rib. First there is thrombus formation within the artery, then signs of circulatory failure in the finger tips, which may eventually progress to gangrene. This clinically may seem to be a gradually progressive affair, though there can be little doubt that it is due to the cumulative effect of small emboli thrown off by the thrombus and lodging in the distal arterioles (Lewis and Pickering, 1934; Eden, 1939; Holling, 1939). Only in the later stages is there diminution and finally obliteration of the pulse at the wrist, then extending from the periphery upwards. This is the usual course of events, but sometimes a larger embolus will cause sudden, severe ischæmia. The earliest symptoms of this syndrome, numbness and pallor in the finger tips, are intermittent.

A comparable sequence of events would account either for progressive or sudden infarction of the occipital lobes in cases of basilar or vertebral thrombosis. The likely time for this occurrence would be before occlusion is complete, while a surface of recent thrombus is exposed to the blood-

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stream, and in this connection it may be observed that loss of vision in several of the cases we have considered has been followed after an interval by symptoms of basilar occlusion.

A third possible sequence of events in the cases with basilar occlusion would be extension of thrombus from the basilar throughout the posterior cerebral arteries into the calcarine branches. This possibility is not supported by the available facts of pathological observation, and it would be difficult to explain on this basis the absence in most cases of any clinical evidence of thrombosis of the other branches of the posterior cerebral arteries, of which the symptoms have been fully reviewed by Masson (1923). Furthermore, it seems very improbable that such an extension of thrombus would arrive at both calcarine arteries at the same time, and only in this way could one explain the simultaneous onset of blindness in the two fields which is observed in most cases.

We have next to consider the pathogenesis in the 5 cases in our material in which the visual loss was not sudden, but progressive. The most reliable history of this was in the case of Holmes (1934). Such cases are comparable with those of progressive hemiplegia from internal carotid occlusion, and it has been suggested (Symonds, 1957) that the cause is a progressive, ischæmic necrosis. It might alternatively be the cumulative effect of repeated small emboli. This question, whether the pathogenesis of cerebral infarction secondary to stenosis or occlusion of the arterial mains supplying the Circle of Willis is due to ischæmia, extension of thrombosis, or embolism, clearly deserves further investigation for it is of more than academic importance. If continued thrombus formation in the basilar or vertebral arteries, with resultant embolism, is the common cause of blindness from occipital lobe infarction, this disaster might be averted by the continued administration of anti-coagulants. This has been advocated by Millikan, Siekert and Shick (1955) as a general rule for patients with symptoms indicating intermittent insufficiency of the basilar system, and they have reported cessation of these symptoms in a number of cases.

Summary

A review is presented of 29 cases from the literature in which loss of vision in both halves of the visual fields was associated with the post-mortem observation of bilateral occipital lobe infarction. The clinical data of 20 cases from the literature in which comparable symptoms were observed without post-mortem examination are also summarized.

Nine further observations of the syndrome are presented, 4 with post-mortem confirmation, and the material thus derived from 58 cases is discussed.

The loss of vision may be sudden or gradual. Both half-fields may be

affected at the same time or in succession. The common mode of onset is a sudden loss of both half-fields.

The most frequent prodromal symptoms are attacks of vertigo, and transient episodes of visual impairment.

Permanent blindness occurs in a quarter of the cases.

The pattern of the visual fields when there is partial sparing or recovery of vision indicates that the area most often preserved corresponds with, or lies within, a circle extending to about 10 degrees from the fixation points. In the more peripheral parts of the visual fields the sectors adjacent to the vertical meridian are not infrequently spared when there is loss of the remainder. Selective loss of central vision is a rare, but well authenticated, occurrence.

Psychological disorder, including spatial disorientation, visual agnosia, denial of blindness, visual hallucinations and other symptoms is an inconstant, but sometimes conspicuous, feature of the syndrome.

The anatomical basis of the visual field defects is discussed, and the arterial blood supply to the visual cortex and optic radiations is considered in relation to the clinical and pathological data.

The pathogenesis of the syndrome is discussed with especial reference to the occurrence of simultaneous loss of vision in both halves of the visual fields, and the post-mortem finding, in a significant proportion of the cases in which full pathological data are available, of thrombosis in the basilar or vertebral arteries. The conclusion is drawn that the most frequent cause of bilateral occipital lobe infarction is embolism of the calcarine arteries. The emboli may result from valvular disease of the heart, auricular fibrillation or coronary thrombosis, but are more often derived from thrombus formed within the basilar or vertebral arteries as the result of atherosclerosis.

In addition to the acknowledgments already made we owe our thanks to the editors of the following journals for permission to reproduce figures from their pages: *Revue Neurologique; Archives of Ophthalmology; American Journal of Ophthalmology; Proceedings of the Royal Society of Medicine.* We are likewise indebted for figures 2 and 4 to the Journals in which they originally appeared. We are especially grateful to Dr. J. G. Greenfield for the drawings reproduced in fig. 12.

REFERENCES

ABBIE, A. A. (1938) *Med. J. Aust.*, **2**, 199.
ALLYN, G. W. (1896) *Arch. Ophthal., N.Y.*, **25**, 206.
BEEVOR, C. E. (1909) *Phil. Trans. B.*, **200**, 1.
—— and COLLIER, J. (1904) *Brain*, **27**, 153.
BERGER, O. (1885) *Breslau. aerztl. Z.*, **7**, 1, 28, 37 and 51.
BIEMOND, A. (1951) *Brain*, **74**, 300.
BOUVERET, L. (1887) *Lyon med.*, **56**, 337.
BRAMWELL, B., BOLTON, J. S., and ROBINSON, W. (1915) *Brain*, **38**, 447.

XUM

DÉJERINE, J. (1901) "Anatomie des Centres Nerveux." Paris.
——, and VIALET, N. (1893) *C.R. Soc. Biol., Paris*, **5,** 983.
DENNY-BROWN, D. (1953) *Bull. New Engl. med. Cent.*, **15,** 53.
EDEN, K. C. (1939) *Brit. J. Surg.*, **27,** 111.
FOIX, C., and SCHIFF-WERTHEIMER, M. (1925) *Rev. neurol.*, **32** (i), 361.
FÖRSTER, O. (1890) *v. Graefes Arch. Ophthal.*, **36,** 94.
GROENOUW, A. (1892) *Arch. Psychiat. Nervenkr.*, **23,** 339.
HEMPHILL, R. E. (1941) *Irish J. med. Sci.* p. 28.
HENSCHEN, S. E. (1900) *XIII Congr. Internat. de Med., Paris*, **12,** 232.
HOLLING, H. E. (1939) *Guy's Hosp. Rep.*, **89,** 285.
HOLMES, G. (1918) *Brit. J. Ophthal.*, **2,** 353.
—— (1931) *Brain*, **54,** 470.
—— (1934) *Jb. Psychiat. Neurol.*, **51,** 39. Reprinted in Selected Papers of Sir Gordon Holmes. 1956. London. p. 195.
HUTCHINSON, E. C., and YATES, P. O. (1956) *Brain*, **79,** 319.
——, —— (1957) *Lancet*, i, 2.
JACQUEAU, A. (1900) *XIII Cong. Internat. de Med., Paris*, **12,** 250.
KEARNS, T. P., WAGENER, H. P., and MILLIKAN, C. H. (1955) *Arch. Ophthalmol., N.Y.*, **53,** 560.
KNIES, M. (1896) *Z. Biol.*, **34,** 125.
KUBIK, C. S., and ADAMS, R. D. (1946) *Brain*, **69,** 73.
KUSTERMANN, K. (1897) *Mschr. Psychiat. Neurol.*, **2,** 335.
LAGRANGE, H., BERTRAND, I., and GARCIN, R. (1929) *Rev. neurol.*, **36** (i), 417.
LAWRENCE, G. A. (1952) *Arch. Ophthal., N.Y.*, **48,** 602.
LEWIS, T., and PICKERING, G. (1934) *Clin. Sci.*, **1,** 327.
LISTER, W. T., and HOLMES, G. (1916) *Proc. R. Soc. Med.*, **9** (Sect. Ophthal.), 57.
LUNZ, M. A. (1897) *Dtsch. m. Wschr.*, **23,** 610.
MCDONALD, P. R. (1943) *Arch. Ophthal., N.Y.*, **29,** 92.
MAGITOT, A., and HARTMANN, E. (1926) *Bull. Soc. Ophtal., Paris.*, **38,** 427.
MAN, H. X., and GRUNER, J. (1952) *Bull. Soc. franc. Ophtal.*, **65,** 127 and 134.
MARIE, P., and LÉRI, A. (1911) *Bull. Soc. med. Hop., Paris.*, **31,** 877.
MASSON, A. (1923) Thèse de Paris.
MELLA, H. (1922) *J. nerv. ment. Dis.*, **56,** 563.
MEYER, O. (1900) *Mschr. Psychiat. Neurol.*, **8,** 440.
MILLIKAN, C. H., and SIEKERT, R. G. (1955) *Proc. Mayo Clin.*, **30,** 61.
——, ——, and SHICK, R. M. (1955) *Proc. Mayo Clin.*, **30,** 116.
V. MONAKOW, C. (1885) *Arch. Psychiat. Nervenkr.*, **16,** 317.
OULMONT, P. (1889) *Gaz. hebd. Med. Chir.*, **26,** 607.
PETERS, A. (1896) *Arch. Augenheilk.*, **32,** 175.
RAVIART, G., and CANNAC, R. (1909) *Echo med. Nord*, **13,** 25.
RAYMOND, F., LEJONNE, P., and GALEZOWSKI, J. (1906) *Rev. neurol.*, **14,** 680.
REDLICH, F. C., and DORSEY, J. F. (1945) *Arch, Neurol. Psychiat., Chicago*, **53,** 407.
REESE, F. M. (1954) *Amer. J. Ophthal.*, **38,** 44.
RILEY, H. A., YASKIN, J. C., RIGGS, M. E., and TORNEY, A. S. (1943) *N.Y. St. J. Med.*, **43,** 1619.
RIMBAUD, L., CHARDONNEAU, J., and BALMES, A. (1932) *Rev. Oto-Neuro-Ophtal.*, **10,** 687.
ROSS, J. V. M. (1949) *Amer. J. Ophthal.*, **32,** 1588.
SANDIFER, P. H. (1946) *Brain*, **69,** 122.
SCHWEIGGER, C. (1891) *Arch. Augenheilk.*, **22,** 336.
SHELLSHEAR, J. L. (1927) *Brain*, **50,** 236.
SILVERSIDES, J. L. (1954) *Proc. R. Soc. Med.*, **47,** 290.

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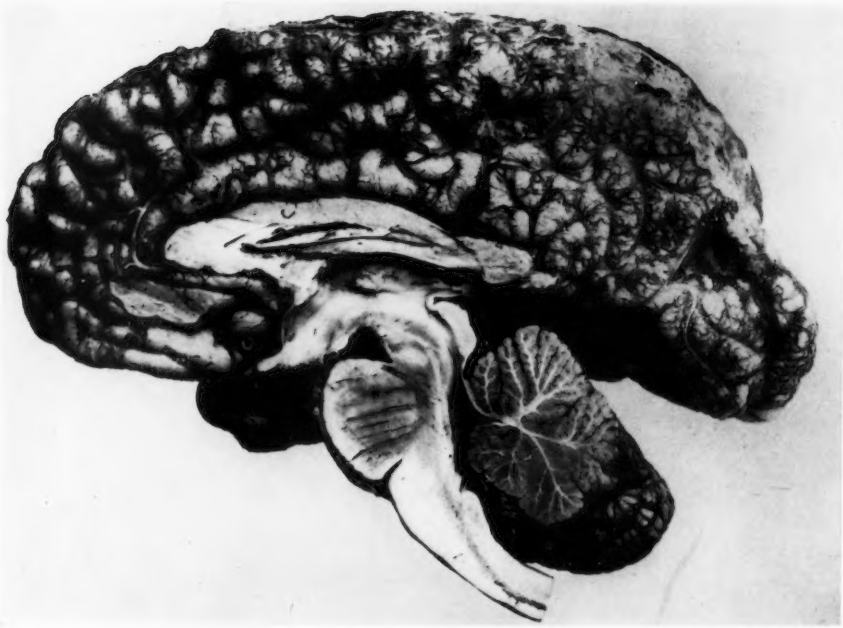

FIG. 9.

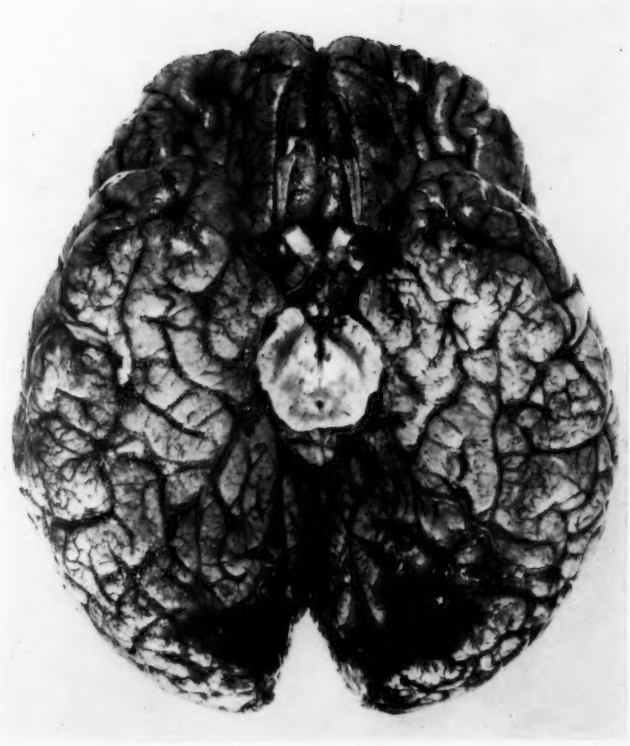

FIG. 10.

To illustrate article by Charles Symons and Ian Mackenzie.

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SPALDING, J. M. K. (1952*a*) *J. Neurol. Neurosurg. Psychiat.*, **15**, 99.
—— (1952*b*) *J. Neurol. Neurosurg. Psychiat.*, **15**, 169.
STEINER, A. A. (1951) *Amer. J. Ophthal.*, **34**, 1170.
SYMONDS, C. (1948) *Rev. neurol.*, **80**, 401.
—— (1957) *in* Williams' "Modern Trends in Neurology," 2nd Series, London. p. 91.
TERRIEN, F. (1938) *Prog. med.*, **65**, 575.
VANDER EECKEN, H. M., and ADAMS, R. D. (1953) *J. Neuropath.*, **12**, 132.
VIALET, N. (1893) "Les Centres Cérébraux de la Vision." Paris.
WAGMAN, O. H. (1952) *New Engl. J. Med.*, **247**, 7.
WORSTER-DROUGHT, C. (1928) *Proc. R. Soc. Med.*, **21**, 1511.

LEGENDS FOR PLATE

PLATE LVI

FIG. 9 (*Case* 1).—Medial aspect of right hemisphere, showing destruction of visual cortex.

FIG. 10 (*Case* 2).—Brain showing destruction of medial aspect of occipital lobes.

THE ASSOCIATION OF CERVICAL SPONDYLOSIS AND DISSEMINATED SCLEROSIS

BY

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INTRODUCTION

IN an earlier paper (Brain, Northfield, and Wilkinson, 1952) we drew attention to some of the diagnostic problems of cervical spondylosis. It was natural that, before the production of myelopathy by cervical spondylosis had been recognized, other diagnoses should have been made to explain the nervous symptoms actually caused by the spondylosis. We therefore discussed chiefly the diagnosis of cervical myelopathy due to spondylosis from those other nervous disorders which it is most likely to simulate, especially disseminated sclerosis, amyotrophic lateral sclerosis, tumour of the spinal cord, syringomyelia, subacute combined degeneration, and other conditions causing progressive spastic paraplegia. We also pointed out that the radicular symptoms of cervical spondylosis might simulate myocardial infarction or lesions of the brachial plexus or peripheral nerves of the upper limbs.

We added that since cervical spondylosis is not uncommon after middle life, and may be symptomless, there is a danger that the discovery on radiography of cervical spondylosis in a patient suffering from some other disorder may lead to the mistaken attribution of the symptoms to the cervical spondylosis. Now that the existence of cervical spondylosis as a cause of symptoms of disorders of the spinal cord and nerve roots is well known, this diagnostic problem has become much more frequent.

In this paper we report 17 patients suffering from cervical spondylosis in whom a diagnosis of disseminated sclerosis was also made. In 2 cases the diagnosis was verified by post-mortem examination. In a further 9 cases it was established by the presence of characteristic symptoms and signs of lesions above the level of the spinal cord. In one further case (No. 12) although there were no abnormal signs above the level of the spinal cord changes characteristic of disseminated sclerosis were present in the cerebrospinal fluid. Thus in 12 cases the diagnosis of disseminated sclerosis was beyond doubt. In the remaining 5 cases

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although cervical spondylosis was present and the abnormal physical signs were limited to the spinal cord we thought on clinical grounds that the patient probably had disseminated sclerosis as well. We have included these because they illustrate the difficulty of making a correct diagnosis in such cases.

Case Reports

Case 1.—W. D., male, aged 54. Admitted to London Hospital on five occasions: 10.9.47, 19.12.47, 21.7.49, 25.4.51 and 20.7.52. L.H. No. 31576/49. P.M. No. 109/53. Died 11.3.53.

History.—Two and a half years before his first admission he noticed that his right leg was weak and that he dragged his right foot. Six months later he became impotent and one year before his admission he developed precipitancy of micturition, a tingling sensation in his right foot and hand, and deadness in his right foot.

In 1946 he was admitted to another hospital where he was found to have signs suggestive of cord compression at C5–6, and X-rays of the cervical spine showed spondylotic changes maximal at C5–6. A myelogram showed a filling defect at the C5–6 level. After the myelogram he developed retention of urine.

He was admitted to the London Hospital for the first time on 10.11.47, and on examination his cranial nerves were normal. There was slight weakness of flexion of the fingers on the right, and the right supinator and triceps jerks were diminished. The right lower limb was weak, both knee and ankle jerks were exaggerated and both plantars extensor. The abdominal reflexes were absent. Sensation was normal in the upper and lower limbs. All movements of the cervical spine were restricted.

Investigations.—C.S.F. Initial pressure 180 mm. Slow rise and fall on jugular compression. Cells 3 per c.mm.; protein 30 mg. per cent; W.R. negative and Lange 001000.

He was discharged on 30.9.47, at which time he was having daily bladder washouts. A suprapubic catheter was inserted on 28.10.47. His condition did not improve and he was readmitted on 20.1.48. *A right hemilaminectomy* was done by Mr. Northfield on 28.1.48. The laminæ of C6, 7, 5 and part of C4 were removed. Laterally the lamina of C5 was removed as far as the articular processes, and the intervertebral foramen was opened up fully.

Arising from the posterior surface of C5 and its lower lip there was a pronounced dome-shaped swelling measuring 1 cm. across and about 0·3 cm. high at the summit, and covered on its surface by shiny fibro-cartilage, such as is seen in the lumbar region over a prolapsed intervertebral disc. Laterally it extended as far as the intervertebral foramen and medially at least half across the spinal canal. The sixth nerve root was riding over it passing so that one-third of the protrusion lay in the superior angle of the converging nerve, and the theca and the nerve root appeared to be displaced posteriorly and caudally. The dura was opened but no abnormality was found other than the protrusion which was easily palpable. The cord appeared normal. The prominence was removed completely and it proved to be fibro-cartilagenous superficially, but it was mainly cancellous bone and, when removed, a crack was found which passed down into the disc corresponding approximately to the lowest border of the protrusion. When the protrusion had been removed the sixth nerve root was more mobile.

Following the laminectomy there was a slight improvement in his lower limbs, but none in his bladder or bowel functions. When he was admitted to hospital a year later there was very little change in his physical signs, except that the weakness of the triceps had become more marked, his lower limbs more spastic, and he had impaired

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postural and vibration sense in his feet. A myelogram, done on 25.8.49, showed a small filling defect opposite the disc space between C4 and 5.

During the last two years of his life there was a progressive deterioration in his condition, and he had increasing difficulty in walking, until a year before his death he was able to manage only a few steps with the aid of a stick. His left leg had become numb, and his right hand clumsy, and he had difficulty in feeling and holding objects. On examination the physical signs showed a further change. His cranial nerves were normal apart from nystagmus on looking upwards. There was a slight increase of tone in the right upper limb, with marked distal wasting and weakness and clumsiness in doing fine movements. The supinator-jerks, triceps-jerks and right biceps-jerk were absent, and the left biceps-jerk diminished. There was no sensory loss in the upper limbs. In the lower limbs there was generalized wasting and spastic weakness, more marked on the right than the left, with exaggerated tendon reflexes, absent abdominal reflexes and extensor plantar responses. There was an indefinite analgesia and impaired position sense and vibration sense in the lower limbs.

His last admission to hospital was in July 1952. At that time he was unable to walk and had painful flexor spasms. In September 1952 a laminectomy (thoracic 10–12) was done and the sacral and lumbar vertebral roots were cut on the right side. This relieved the flexor spasms, but his condition continued to deteriorate and he died on 11.3.53.

Pathological examination.—P.M. 109/53. *Summary of necropsy:* Cardiac infarction. Coronary thrombosis. Chronic pyelonephritis. Prostatic and urethral abscesses. Cervical spondylosis. Disseminated sclerosis. Recent infarct in posterior wall of left ventricle and adjacent intervertebral septum. Considerable general atheroma. Bilateral pleural effusions with œdema and partial collapse of basal parts of both lower lobes. Obsolete tuberculosis of apices of both upper lobes.

Lordosis of cervical spine with concavity centred at level of sixth vertebra. Postero-lateral protrusions of intervertebral disc, up to 0·2 cm. high on right and 0·1 cm. on left, between C4 and C5. Similar protrusion, forming an irregular transverse bar up to 0·2 cm. high between C5 and C6. Firm union of dura over bodies of fifth and sixth vertebræ. Considerable narrowing of intervertebral foramina corresponding to fifth, sixth and seventh cervical roots, especially at right sixth. Kinking of seventh right cervical root upwards and posteriorly over lateral disc protrusion. No deformation of discs below level of C6.

Central nervous system. Macroscopic examination. — Brain: No external abnormality. Four clearly defined grey plaques of sclerosis distributed in cerebral grey and white matter, one in ventral border of pons and two in upper medulla oblongata.

Spinal cord: Considerable diffuse atrophy of cord with flattening of posterior columns, especially in cervical segments. Flattening in antero-posterior dimensions of sixth cervical segment. Extensive grey sclerosis of white matter throughout cord, consistently involving posterior columns but varying in extent elsewhere at different levels.

Microscopic examination.—Brain: Glial plaques with demyelination in deep cortex and adjacent white matter of left and right superior parietal lobule, right superior temporal and left middle frontal convolutions, in basal part of pons and in medulla oblongata. No evidence of active progression, and very few scanty lymphocytic adventitial infiltration of a few included blood vessels. A Marchi preparation of the lower medulla shows a small patch of active degeneration at the posterior border.

Spinal cord: Preparations were made from all cervical segments except the first; thoracic segments 1, 4, 6, 8 and 9; lumbar 1 and sacral 2. All these were variably involved in demyelination and gliosis. The changes were minimal in C2 and 3.

The area involved by plaque formation increases in successive segments to attain a maximum in C6 and 7 (fig. 1, Plate LVII). Both C8 and Th1 are similarly affected but the more caudal segments Th4, 6 and 8 show a decrease. Th9 is, however, involved to a degree comparable with that in the lower cervical segments. The lumbar and sacral segments again show some diminution in the degree of demyelination. Marchi preparations of Th8 provide evidence of active stages in the demyelinating process. No changes directly attributable to the cervical spondylosis can be detected in the relevant cervical segments.

Case 2.—J. S., male, aged 61. Admitted London Hospital 13.11.50 and 3.1.52. L.H. No. 47966/50. P.M. No. 376/52.

History.—Three years ago he had an accident at work. One end of the heavy iron pontoon bridge section he was carrying was dropped leaving him to carry most of the weight. Shortly after this accident he complained of pain in his back and legs and developed a hernia. The hernia was treated with a truss. The pain in his lower limbs became worse and in addition he developed weakness, numbness and tingling in his legs. His legs gradually became weaker, he had severe pain in the left hip and he was unable to lift heavy objects. By October 1950 he could only walk 100 yards using sticks and had frequency of micturition. On 16.11.50 a cup arthroplasty was done and following this he developed retention of urine.

Over the next few months his legs became increasingly weak and at night he had painful flexor spasms. His legs became numb and he had continuous dribbling from his penis and fæcal incontinence. Four months before his last admission his hands started to get weak and two months later they became cold and numb and he was unable to feel objects properly.

He was readmitted two days before his death. At that time he was ill and wasted, had a right lower lobe pneumonia and a urinary infection.

Examination.—In his central nervous system there was pallor of both optic discs and nystagmoid jerks on looking to the left. The other cranial nerves were normal. There was spastic weakness of both upper limbs and wasting of the small muscles of the hands. The lower limbs were fixed in flexion and there was no voluntary movement. All the tendon reflexes were exaggerated with patella and ankle clonus, the plantar responses were extensor and the abdominal reflexes were absent. There was a patchy sensory loss in the upper limbs and impairment to all forms of sensation below thoracic 2.

Investigations.—Lumbar puncture: Initial pressure 140 mm. with free rise and fall on jugular compression. Protein 40 mg. per 100 c.c. Cells 7 lymphocytes per c.mm. W.R. negative, Lange 532221.

X-ray cervical spine: Cervical spondylosis present at C5–6 (fig. 5, Plate LIX). Lack of alignment of the bodies of C4–5. The posterior intervertebral joints in the lower cervical spine show degenerative changes.

X-ray dorsal spine: Severe degenerative changes in all areas with upper dorsal scoliosis.

His condition rapidly deteriorated and he died on 17.10.52.

Pathological examination.—Summary of necropsy: P.M. 376/1952. Pulmonary œdema. Disseminated sclerosis. Cervical spondylosis.

Cervical spine: Posterior protrusion 0·5 cm. by 0·1 cm. thick of intervertebral disc between C5 and 6; similar smaller protrusion at C6–7. Several small disc protrusions in upper thoracic spine.

Macroscopic appearance of central nervous system after fixation.—Brain: Slight opacity of leptomeninges over cerebral convexities and in cisterna ambiens.

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Considerable atheroma of main cerebral arteries. Slight dilatation of lateral ventricles. Numerous pale or grey granular plaques of demyelination distributed through cerebral white matter, especially in region of temporal horns, and throughout brain-stem.

Spinal cord: Shallow indentations on anterior surface opposite cervical intervertebral discs 3–4, 4–5 and 5–6. Grooving of right second, third and fourth roots posteriorly by vertebral artery. Texture of cord abnormally tough on section.

Microscopic examination.—Brain: Sections at different levels of the brain demonstrate plaques of demyelination as observed with the naked eye. Some are clearly of considerable age and appear quiescent: others show evidence of expansion, being fringed with foam cells and having conspicuous cups of cellular infiltration about the included blood vessels. In Marchi preparations through the mid-brain there are several very early plaques in which active demyelination is obvious and generalized.

Spinal cord: Sections through each cervical segment show intensification of the demyelination from above down (fig. 2, Plate LVIII). In the upper segments the posterior columns have undergone degeneration and asymmetrical plaques occupy the ventral parts of the lateral columns. At the fourth segment one lateral column only is affected. In the fifth segment both lateral columns are extensively involved and many foam cells are scattered throughout these areas. The degeneration is still wider in the lateral columns in the sixth segment. There is no obvious deformation of the cervical cord nor any evidence of a destructive process that could be directly referred to the mechanical effects of spondylosis.

More caudal segments of the cord show little change in the picture by comparison with the lower cervical segments, though the extent of the degeneration and its topography varies slightly at different levels. In the first lumbar segment, for example, the degeneration appears to be almost complete.

Case 3.—H. B., male, aged 59. Admitted to the London Hospital on three occasions: 1937, 1955 and 1956. L.H. No. 24274/55.

History.—In 1937 he was admitted to the London Hospital under the care of Dr. Riddoch, complaining of weakness and pins and needles in the right leg, and some difficulty in micturition. A diagnosis of disseminated sclerosis was made.

Since then he has continued to drag his right leg which has become weaker. Three years ago he started to get pain in the neck and both shoulders, which was made worse by moving his neck. The pain occasionally extended down the outer side of his right arm.

In August 1955 he was bending to pick up a piece of wood, when he experienced a sudden severe pain in the back of his neck. This extended down both arms. His limbs felt weak, and he could hardly move them. He was still complaining of severe pain in his neck and arms at the time of admission.

General health good. Bowels constipated. Micturition—some frequency and hesitancy.

Examination (31.8.55).—Healthy looking man. Slight euphoria.

Cervical spine: All movements limited and painful.

Cranial nerves: Fundi—R. disc normal, L. pale. Slight nystagmus to right and left. Jaw-jerk brisk but not exaggerated. Other cranial nerves normal.

Motor system: Upper limbs—weakness of abduction and adduction of the right shoulders with some generalized wasting of the right arm, most marked in the supraspinatus. No fasciculation seen. Slight ataxia in the finger-nose test. *Lower limbs*—marked spastic weakness of the right lower limb, most severe distally. The left leg was weak only at the hip, and there was only slight ataxia in the heel-knee test on both sides.

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Sensory system: Subjective sensory loss to pin-prick over the right half of the body below the clavicle. Postural and vibration sense normal in upper limbs. Vibration sense absent in the right lower limb and impaired in the left. Position sense impaired in right lower limb and normal in the left.

Reflexes: Biceps-jerks and supinator-jerks brisker left than right, triceps-jerks present and equal, right knee-jerk brisker than left, ankle-jerks present and equal. Abdominal reflexes—left upper present, others absent. Plantar responses extensor.

Investigations.—X-ray cervical spine: Gross cervical spondylosis maximal at C4–5, C5–6, C6–7 disc spaces, where there is reduction of disc space, lipping and surrounding sclerosis. The neurocentral joints also show osteoarthritic changes and osteophytic protrusion into the intervertebral foramina.

He was fitted with a collar which relieved the pain in his neck and he was discharged home.

He continued to attend out-patients and in November 1955 he said that he had had an attack of blindness of sudden onset in his right eye. This had lasted for about five minutes and his vision had returned to normal in about twenty minutes. About this time he was retired from his work as a Company Secretary, on pension. As a result of this he became depressed.

In November 1956 he developed severe low backache with pain radiating down his left leg. The pain was so incapacitating that he was readmitted to the London Hospital in December 1956.

Examination (December 1956).—He was found to have pallor of both discs, more marked on the right than the left. Visual acuity was 6/6 in both eyes, the other cranial nerves were normal.

Motor system: Upper limbs—slight wasting and weakness on the right with ataxia in the finger-nose test. *Lower limbs*—gross bilateral weakness with spasticity more marked on the right than the left. Pain on straight leg raising to 10 degrees on left.

Reflexes: Brisker left than right in upper limbs. Left ankle-jerk absent. Plantars extensor. Abdominals absent.

Sensation: Hyperæsthesia to pin-prick, hot and cold, and vibration sense over left side of the body. B.P. 160/100. Heart sounds normal.

Investigations.—X-ray lumbar spine. Spondylotic changes are present in the lumbar spine and the body of L1 is shifted back on L2. The disc between L5 and S1 is narrow, particularly on the left and here there is sclerosis of its bony margins with osteophyte formation.

He was fitted with a plaster jacket which relieved his pain, but three days later he suddenly developed a left homonymous hemianopia and a weakness and loss of sensation over the whole of the left side of his body, and became confused and disorientated.

The pulsation in the right carotid artery was diminished and the artery was tender on palpation. A diagnosis of thrombosis of the right internal carotid artery was made.

He later developed painful flexor spasms of his left lower limb. These were relieved by an intrathecal injection of alcohol. His condition gradually improved but he still had gross weakness and sensory loss on the left side on his discharge from hospital in March 1957.

Comment.—This patient first developed signs and symptoms of disseminated sclerosis in 1937. The episode of weakness of all four limbs in August 1955 was probably due to the effect of trauma by spondylosis on a cord already damaged by disseminated sclerosis. The thrombosis of the right internal carotid artery caused a further deterioration in his condition, leaving him with a well-marked left-sided hemiparesis and impaired sensation on the left.

XUM

Case 4.—G. F., male, aged 55.

History.—Seven years ago he had attack of dimness of vision which was diagnosed as a retrobulbar neuritis.

Three years ago: onset of unsteadiness on walking and weakness of the legs—the weakness of the legs came on after a feverish illness.

Two years ago: onset of paræsthesiæ in the lower limbs, the left being more affected than the right.

Since then there has been a slow progression of his symptoms—the weakness of his lower limbs has increased, he has been bedridden for the last three months, and he has developed some weakness of his left arm. In the last few months he has had some attacks of double vision.

Micturition and bowel symptoms: On three occasions he has had difficulty in initiating micturition and he has been constipated for the last three years.

Mental state: Throughout his illness he has been anxious and depressed.

Examination.—His speech and articulation were normal. He was myopic. The right optic disc was normal while the left showed primary optic atrophy. V.A. normal on right, finger-counting on left. The pupils and ocular movements were normal and there was no nystagmus. The jaw-jerk was within normal limits and the other cranial nerves were normal. His upper limbs showed no muscular wasting, but there was some general weakness considerably more marked on the left than the right and most obvious in abduction of the shoulders and supination of the forearm; pronation in contrast was good. There was some intention tremor in the right hand. The supinator-jerks were moderately brisk and associated with flexor finger-jerks. The biceps-jerks were rather brisker than the supinator-jerks. The triceps-jerks were relatively diminished especially on the left side. The abdominal reflexes were absent.

In the lower limbs there was slight spasticity associated with considerable weakness, again more marked on the left side than on the right. The knee and ankle jerks were brisk, but not grossly exaggerated, and both plantar reflexes were extensor. There was no sensory loss to light touch or tactile discrimination and no loss of appreciation of passive movement or vibration. To pin-prick there seemed to be some doubtful hypalgesia over the middle and ring fingers of the left hand and below the nipple line on the left side of the trunk.

There was considerable cervical lordosis and dorsal kyphosis to which the cervical lordosis was compensatory.

Investigations.—X-ray cervical spine: Narrowed disc C4–5 with large posterior osteophyte. Slight narrowing C5–6 with a smaller posterior osteophyte.

Myelogram: The available films showed no good view of the cervical region.

C.S.F.: Pressure 10 cm. water. Free rise and fall on jugular compression. Protein 35 mg. per cent. 8 cells per c.mm.

Comment.—This man suffered from two disorders. He had an attack of retrobulbar neuritis in the left eye, and this together with his double vision can be attributed to disseminated sclerosis. On the other hand the relative weakness of certain muscles of the upper limb innervated by the fifth cervical segment of the spinal cord, the asymmetry of the tendon reflexes in the upper limbs, particularly the reduction in the triceps-jerks, and the analgesia over the middle and ring fingers of the left hand, indicate compression of the spinal cord by the disc protrusion shown in X-ray between C4 and 5. The weakness of the upper and lower limbs might be due to either or both of the disorders.

Case 7.—D. G., female, aged 37. Admitted London Hospital 26.6.57. L.H. No. 3568/52.

History.—About ten years ago she began to have low backache and she noticed that she dragged her right leg when she was tired.

XUM

Eight years ago she had an attack of pain, so severe that she fainted and she was admitted to hospital. Her back was manipulated and this relieved the pain but a few months later the pain recurred after a fall downstairs. A further manipulation failed to relieve the symptoms and a lumbar laminectomy was done in 1950. Her symptoms were again relieved for a short time but later recurred and she developed an aching pain in both thighs.

Five years ago she first noticed pain in the right side of her neck. This pain gradually became more severe and extended from the base of her neck, over her shoulder and down to the elbow and hand. On examination in 1953 there was some tenderness over the third, fourth and fifth cervical spines and she had pain on movement of her neck and both triceps-jerks were diminished. An X-ray of the cervical spine showed spondylotic changes in the lower cervical vertebræ with some narrowing of the intervertebral foramen between C5 and 6. She was given a collar and her pain diminished.

The pain in her back persisted and a spinal fusion was done in 1954. Following operation she was put in a plastic jacket. When this was removed she noticed that her right leg was weak and this weakness has persisted.

In February 1955 she complained that she had numbness and loss of sensation in the tip of her right thumb in addition to the pain in her neck and arm. On examination there was tenderness in the upper cervical region, all movements of the upper cervical spine particularly rotation and lateral flexion to the left were painful. The biceps and supinator jerks were brisk and the right triceps-jerk was diminished. There was slight impairment to light touch over the tip of the right thumb. The pain diminished after eight weeks in bed.

When seen in July 1956 she said that she had had more pain in the cervical and lumbar regions. The pain radiated down both arms and when she woke in the morning the fingers of the right hand were numb and she had a feeling like electricity in her finger tips. On examination both triceps-jerks were diminished, the right triceps and right grip were weak and she had some hyperæsthesia over the ulnar margin of the right hand. Later in the year she was found to have diminution of the right biceps and triceps jerks.

January 1957 the numbness of right thumb and index finger became more marked and spread over the hand and the whole arm and prevented her from typing.

Examination (April 1957).—The cranial nerves were normal. There was slight generalized tenderness and weakness of the right upper limb. The right biceps and supinator jerks were diminished and there was relative analgesia over the ulnar border and fingers of the right hand. There was a generalized weakness of the right lower limb probably due to pain. The knee-jerks and left ankle-jerk were normal, the right ankle-jerk diminished, plantar responses flexor.

On 13.4.57 she was admitted to hospital and the following day cervical spine traction with a weight of 15 lb. was applied. This was uncomfortable and was discontinued.

On 15.4.57 Crutchfield's skull traction was applied under local anæsthesia and a weight of 12 lb. was put on.

On 22.4.57 after she had been on skull traction for a week she complained of a very acute pain in the left eye and pain across the forehead and the top of the head.

On 1.5.57 she complained of generalized discomfort and said that her right arm and leg felt numb and that she had an aching pain in her right arm, shoulder and leg. The pain over her left eye persisted. On examination there was some tenderness over the second cervical vertebra. There was a generalized weakness of the right upper limb and the right triceps-jerk was absent. In addition she had a diffuse and indefinite hypoæsthesia over the right arm and shoulder. The tone and power were normal in the lower limbs, the knee and ankle jerks were present and equal

XUM

and both plantars were flexor. Straight leg raising was limited to 40 degrees on the right and 70 degrees on the left.

On 2.5.57 the skull traction was discontinued.

On 6.5.57 the headache became worse and she had a slight nose-bleed.

On 11.5.57 she still complained of left frontal headache and of severe pain in her left eye. At this time the vision in her left eye became blurred and she had photophobia. On examination the fields and fundi were normal and the globe tension was not increased.

14.5.57: She continued to have severe pain in and about the left eye and she complained of some numbness over the distribution of the ophthalmic division of the trigeminal nerve.

On 18.5.57 the vision in her left eye deteriorated, "like a curtain being drawn over the eye," and she was only able to distinguish large objects.

On 21.6.57 a myelogram was done and following this she said she had some swelling of the left side of her face.

23.5.57: VAR 6/6. VAL finger-counting only. Fundi normal. (Diagnosis of D.S. first suggested.) Right pupil reacts normally. Left pupil poor direct reaction, normal consensual reaction.

27.5.57 she was discharged home.

In early June she was seen at Moorfields where the vision in the left eye was 6/60 with a central scotoma and she was found to have extensor plantar responses.

Examination (21.6.57).—Tenderness of both eyeballs on pressure.

Fundi: Right disc slight temporal pallor. Left disc pallor more marked.

VA can just read newspaper on right. Finger-counting on left. Pupils—moderately contracted and equal. The right reacts more briskly than the left. Corneals present and equal. No loss of sensation in trigeminal area. Weakness of right lower face. Palatal reflex diminished. Pharyngeal reflex present. Slight weakness of both sides of palate.

Upper limbs: Generalized weakness of right upper limb with weakness of right grip. Co-ordination normal.

Sensory system: Relative analgesia below C3 extending downwards to Th2. Similar level to cotton-wool. Vibration sense diminished at right wrist. Joint sense normal.

Reflexes: Left biceps and supinator jerks brisker on the right with tendency to inverted radial reflex on the right. Left triceps-jerk normal right diminished. Abdominal reflexes absent.

Motor system: Lower limbs slight relative increase in tone on right. Co-ordination normal.

Sensory system normal.

Reflexes: Both knee-jerks exaggerated. Right ankle-jerk diminished left normal. Plantars extensor.

Neck: Marked cervical lordosis and cervical kyphosis. Upper cervical spine tender on right. All movements limited especially lateral flexion.

Obese. B.P. 100/70.

Small nævus $\frac{1}{3} \times \frac{1}{2}$ in. on inner side of right great toe.

Over the next week the vision in her right eye deteriorated and on 27.6.57 she was only just able to read large print with her right eye and the right disc was swollen. The vision in the left eye had improved and she was able to read large print on that side.

Investigations (29.6.57).—L.P. 180 mm. free rise and fall on jugular compression with neck flexed and extended. Protein 30 mg. per cent. Cells 34 lymphocytes per c.mm.

X-ray cervical spine. Small posterior osteophyte at C6–7. Oblique views show slight posterior-lateral osteophytes narrowing the intervertebral foramen at C6–7 on the right.

A myelogram showed slight disc protrusion at C5–6. No other abnormality seen in the skull except some residual myodil. The optic foramina appear normal.

She was discharged to convalesce and whilst there her condition gradually improved. She was seen again on 16.8.57 and at that time the swelling of her right disc had subsided and the disc had become pale; there was pallor of the left disc also.

The power in the right upper limb had improved and she was able to walk fairly well. The left plantar was still extensor, but the right was equivocal.

Summary.—The patient gives a ten-year history of low backache the pain being unchanged by manipulation, laminectomy or spinal fusion and a five-year history of pain in the neck extending down the right arm to the hand. Six months ago she started to get numbness in her right hand which made typing difficult.

The pain in her neck had been treated by rest, physiotherapy and collars, but had been unaffected by these. Skull traction was tried for two and a half weeks. During the latter part of this time she complained of an aching pain and numbness so the traction was stopped.

A few days later she complained of severe pain in the left frontal region and about ten days later she lost the sight in her left eye and the vision in her right eye became blurred.

When examined six weeks later she could only count fingers with her left eye and the vision in her right eye was blurred. In addition she had signs of disseminated sclerosis involving the spinal cord.

Case 5.—M. D., female, aged 70. Admitted to the London Hospital December 1956.

History.—Twenty-eight years ago she had an attack of double vision and unsteadiness of the legs which lasted for eight months.

Seven years ago her left leg became useless for two months, then gradually got better.

One year ago she developed pain in the left shoulder.

Eight months ago she slipped on the doorstep and cut the back of her head. Six weeks after this she noticed that her hands felt numb and swollen and that she was unable to do much with them. Her walking became difficult and her left leg jumped at night.

For six months she has had urgency and precipitancy of micturition.

P.H.—Eleven years ago she had an attack of diarrhœa for which no cause was found.

Examination.—Cranial nerves normal.

Motor system—upper limbs: no wasting, slight generalized weakness more marked on the left than the right. Symmetrical spastic weakness of both lower limbs.

Reflexes—supinator and biceps jerks exaggerated but less so than triceps-jerks. Brisk flexor finger-jerks. Abdominals absent. Knee and ankle jerks exaggerated. Plantars extensor.

Sensory system—relative analgesia below C5. Loss of tactile discrimination at 1 cm. in left index finger, no loss on right. No postural loss. Vibration felt but diminished below clavicles, absent in lower limbs.

Cervical lordosis, neck movements all limited.

B.P. 230/110. Aortic incompetence.

Investigations.—C.S.F. normal pressure, no block. Cells 2 lymphocytes per c.mm., protein 70 mg. per cent. Lange curve "mildly positive." W.R. negative in blood and C.S.F.

Urine: occasional glycosuria.

Blood sugar: 180 mg. per cent.

XUM

X-rays: marked cervical spondylosis C3, 4, 4, 5, 5, 6 and 6, 7. Maximal movement takes place between C4 and 5 and when neck is flexed (figs. 3 and 4, Plate LIX).

Comment.—The attack of double vision with unsteadiness of the legs twenty years ago and the weakness of the left leg for two months seven years ago make a diagnosis of disseminated sclerosis probable. The recent symptoms came on after a heavy fall on the back of her head which caused forcible flexion of her neck. This is interesting as the X-rays of the cervical spine show that the maximal movement of C4 on C5 occurs when the cervical spine is flexed. The present symptoms appear to be due to the effect of trauma by cervical spondylosis on a cord already damaged by disseminated sclerosis.

Case 8.—N. T., female, aged 42.

History.—Four years ago she fell off an egg box and a few weeks later suddenly developed a cold feeling involving the whole of the left side of the body, even including the side of the nose. This lasted for about three weeks, but left her with a permanent feeling of pins and needles in the left hand. Otherwise she remained well until twenty-one months ago when she was involved in a car accident. The car in which she was riding was run into from behind. She thinks she must have knocked her head, but she does not clearly remember this. However, she was not unconscious. The next day her neck was painful and stiff. A few days later she suddenly noticed that both her legs were weak. This weakness has persisted, though at times it has considerably improved. On the whole, however, it has gradually got worse and now she has great difficulty in walking, the right leg being especially weak. Her right hand has also got weak. She has had no sphincter disturbance and there has never been any disorder of vision. She has had a plaster collar and also a plaster jacket without benefit.

Previous history.—She has had rheumatoid arthritis involving the hands for nine years. Married, one child.

Examination.—Normal intelligence. Speech and articulation normal. Optic discs and pupils normal. Fine nystagmus on looking to right and left. Cranial nerves otherwise normal. Slight wasting of right hand, probably secondary to rheumatoid arthritis, which involves mainly the metacarpal and phalangeal joints, but also interphalangeal joints and wrists of both hands. Weakness of right grip, but otherwise power in both upper limbs generally good. Slight intention tremor, more marked on the right side than left. Spastic weakness of both lower limbs, severe on right, moderate on left.

Reflexes: Biceps-jerks exaggerated and equal. Triceps-jerks relatively diminished, especially on the right. Supinator jerks—left brisker than right which is relatively diminished and associated with a brisk flexor finger-jerk. Knee and ankle jerks—right brisker than left, plantars both extensor, abdominal reflexes absent. No sensory loss.

Gait: Just manages to walk alone dragging spastic right leg. Lateral flexion of neck limited.

Investigations.—X-rays: Cervical spine—slight narrowing of disc space C5–6 with backward displacement of C5 on C6 and posterior osteophyte at this level. Myelogram showed narrowing of spinal theca at this level, and in the A.P. view at C6–7 also.

Comment.—This patient undoubtedly suffers from disseminated sclerosis, the initial hemidysæsthesia and the nystagmus indicating lesions above the level of the foramen magnum. She also has cervical spondylosis with narrowing of spinal theca shown on the myelogram. The first symptom of her disseminated sclerosis occurred shortly after a fall, and the paraplegia, which is now her main complaint, developed a few days after an injury to the neck. Her present clinical picture shows some features of cervical spondylosis and others of disseminated sclerosis, and it is probable that the latter is mainly responsible for her disability.

Case 9.—M. W., female, aged 39. Admitted London Hospital 26.6.57. L.H. No. 10696/57.

History.—Ten years ago while walking along the street her right foot went through a pavement light and she cut and sprained her right ankle. After this she noticed that her right foot was weak and she had frequent falls as a result of this. Her right foot tended to turn outwards and drag, this was most noticeable when she was tired. She has several doctors and her foot was manipulated on five occasions with no real improvement.

Six years ago a thyroidectomy was done as she had been very anxious, overactive and had lost two and a half stones in weight. Following this operation her general condition improved.

Five years ago she began to get severe attacks of abdominal pain and frequency of micturition. Following a myomectomy and later appendicectomy the pains improved but she continued to have frequency. For the last four years she had not felt well and had had no energy.

Two years ago while on holiday she had a heavy fall injuring her right leg again. The muscles up to the knee seemed to go stiff. Her leg was put in plaster for four weeks and when the plaster was taken off her leg felt very stiff and remained so. Since then she had had great difficulty in walking, tending to put her toe down first and over the last few months she has had backache and an aching in both calves.

She still has frequency and some urgency of micturition especially in the mornings, her bowels are regular.

At the time of admission she was only able to walk with assistance.

Examination (29.6.57).—She had severe myopia and both discs were pale. She had nystagmoid jerks right and left, her jaw-jerk was not increased and the other cranial nerves were normal. In the upper limbs the tone and power were normal but there was slight unsteadiness in the finger-nose test on the right. The biceps and supinator jerks were brisk and equal and the triceps-jerks were relatively diminished.

She had a spastic weakness of both lower limbs with exaggerated reflexes and extensor plantar responses. The abdominal reflexes were absent.

There was no sensory loss in the upper limbs but joint sense was slightly impaired in both feet. Her heart, chest and abdomen were normal and her blood pressure 120/80.

Investigation.—Neck: Marked upper dorsal kyphosis. Some limitation of extension of neck and tilting head to right and left.

X-ray of cervical spine showed a slight narrowing of the C5–6 disc space and a posterior osteophyte at this level.

Myelogram (27.6.57): Mild spondylotic changes were present in the cervical region with the most marked filling defect at C5–6.

Comment.—This patient has disseminated sclerosis and cervical spondylosis. The first symptom, weakness of the right leg, came on after a fall. Although her main disability is due to disseminated sclerosis the relative diminution of the triceps-jerks suggests that the spondylosis is playing a part in the production of symptoms.

Case 12.—B. B., female, aged 57.

History.—Seven years ago onset of difficulty in walking.

Five years ago she noticed that her legs were weak on climbing stairs. Since then her legs have gradually become weaker.

Four and a half years ago precipitancy of micturition and occasional incontinence of urine.

Four years ago: On examination she was found to have an early spastic paraplegia.

XUM

X-ray of spine showed slight scoliosis to the left in the cervico-dorsal region and slight osteoarthritis in mid-dorsal and lumbo-sacral region.

Lumbar puncture: Cells 12 lymphocytes, protein 140 mg. per cent, Lange 1223210000, W.R. negative.

Three and three-quarter years ago: A second lumbar puncture was done. On this occasion the results were as follows: cells 4, protein 170 mg. per cent, Lange 1223210000.

Three and a half years ago she started to get a tingling in the left hand and down the trunk and noticed that she could not feel her legs properly. The weakness of her legs became more marked and she developed a tremor of her left hand. The urinary incontinence persisted and in addition she had occasional fæcal incontinence.

Seven months ago she had an attack of influenza, and after this she noticed her legs were weaker and she had occasional flexor spasms. In addition she had some dysphagia and her neck was apt to be stiff and painful.

Examination.—Her optic discs and cranial nerves were normal except for slight asymmetrical movement of the soft palate and exaggeration of the jaw-jerk. Motor system—there was a slight general weakness of the left upper limb without wasting or ataxia, and spastic weakness of both lower limbs, especially the left, with exaggerated tendon-jerks everywhere, absent abdominal reflexes and bilateral extensor plantar responses.

Sensory system—appreciation of light touch was generally diminished over both lower limbs, and in the upper limbs there was a suggestion of a level at the junction of the fifth and sixth cervical dermatomes. Appreciation of pin-prick was progressively impaired from above downwards with a level between C2 and C3 and with some sacral sparing on the right side. Thermoanæsthesia was equally extensive with a similar distribution and upper level, though the loss was not absolute over the outer borders of the arm and shoulders. Vibration was just felt on the shins but almost absent below the costal margins and above this was not normally appreciated until the clavicles were reached. Postural sense was normal.

She had a slight cervico-dorsal scoliosis and a cervical lordosis with an upper dorsal kyphosis and her neck movements especially lateral flexion, were somewhat limited and slightly painful.

Investigation (November 1951).—X-ray of cervical spine showed well-marked osteophytosis between C5 and 6.

Comment.—The clinical picture is predominantly that of disseminated sclerosis, the points in favour of this being the long and fluctuating history (seven years), the tendency to become worse after febrile illnesses, the history of urinary incontinence and occasional fæcal incontinence, the extensive type of sensory loss and the abnormal C.S.F.

The symptoms of pain and stiffness in the neck, the upper dorsal kyphosis and limitation of neck movements, the high C.S.F. protein and X-ray changes between C5 and 6 indicate the presence of spondylosis. The spastic paraplegia could be due to either but is likely to be mainly the result of the disseminated sclerosis.

In this case although the main disability is due to disseminated sclerosis the picture has been modified more recently by the addition of symptoms and signs due to cervical spondylosis.

Case 13.—T. T., male, aged 47. Admitted to the London Hospital 30.10.56. L.H. No. 32384/56.

History.—Eleven years ago he developed pain in the lower part of his back and his legs became weak. The right leg was affected before the left, and the weakness gradually progressed until the time of admission when he had difficulty in walking.

Ten years ago his arms began to get clumsy and weak and he noticed numbness in

the tips of his fingers and toes. He has had occasional stiffness of the neck, but no severe pain.

No disorder of micturition, bowels constipated.

No history of injury to the back or the neck.

P.H.—Meningitis in 1942.

Examination.—Cranial nerves normal.

Motor system—spastic weakness of all four limbs, severe in right lower limb and moderate in left lower limb and right arm. Slight weakness only in left upper limb. Co-ordination normal.

Reflexes—biceps, knee and ankle jerks all exaggerated, plantars extensor. Both triceps jerks diminished. Supinator jerks inverted with marked finger flexion. Repeated elicitation of the right supinator-jerk caused increasing reflex flexion of the right middle finger. Abdominals present and equal.

Sensory system—doubtful level to dragged pin C6–7. Two-point discrimination impaired in right hand. No postural loss in arms. Marked postural and vibration loss in right big toe and slight loss in left big toe.

Investigations.—C.S.F.: pressure 120 mm. free rise and fall on jugular compression with neck in flexion, minimal rise and fall with neck extended. Cells 7 per c.mm. Protein 55 mg. per 100 ml. W.R. negative. Lange 001100.

X-ray cervical spine: reduction in disc space between the bodies C5–6 and C6–7, anterior and posterior osteophyte formation is present.

Cisternal myelogram (7.11.56)*:* spondylotic bars between C5–6 and C4–5 with lack of filling of nerve roots on both sides. Posterior osteophyte formation between the bodies of C5–6 is protruding into and breaking this myodil column on both flexion and extension (figs. 6 and 7, Plates LIX and LX).

Operation (21.11.56).—Mr. Northfield: Laminectomy C5, 6 and section of ligamenta denticulata.

Marked disc protrusion at disc between C5 and 6. The intervertebral foramen of C6 on the right was decompressed. The arachnoid was milky and the vessels appeared narrowed and the cord was slightly compressed opposite the C5–6 disc.

Following operation there was very little change in the signs in his upper limbs but the power in his legs improved slightly.

Comment.—This patient gave a long history of difficulty in walking and of weakness of the arms beginning at the age of 36. At operation he was found to have a disc protrusion between C5 and 6. Following the operation there was very little improvement in his condition and it was thought that his symptoms were due to both disseminated sclerosis and cervical spondylosis.

Case 15.—M. M., female, aged 41. Admitted London Hospital 18.6.54. L.H. No. 22805/54.

History.—Two years ago fell feet first down some stairs. Three weeks later noticed a tingling sensation in her left knee, this spread down her leg and at this time she was admitted to another hospital where the c.s.f. was found to be normal in every respect. X-ray of the cervical spine showed degenerative changes in the intervertebral disc at C5–6 with some osteophytosis in all adjacent vertebral body margins.

Eighteen months ago she noticed a similar feeling in her right leg and a year ago the right leg became stiff and the tingling feeling involved both limbs extending up to the waist.

One year ago: For two weeks had a burning girdle pain at the level of the costal margin accompanied by itching.

Nine months: Precipitancy of micturition and cramps at night. For several months she has had pains in the neck especially after movement.

XUM

Three months before admission to the London Hospital a second lumbar puncture was done. Pressure 120 mm., free rise and fall on jugular compression. Cells less than 1 per c.mm. Protein 20 mg. per cent. Lange 000000. W.R. negative. At the time of admission to the London Hospital she was unable to walk without a stick and had had some tingling of her upper limbs.

Examination.—Her cranial nerves were normal except for an exaggerated jaw-jerk.

Motor system: In the upper limbs there was no weakness, wasting or ataxia. All the tendon-jerks were brisk, but the left triceps-jerk was relatively diminished. The abdominal reflexes were absent except for a flicker on the right side. There was spastic weakness of both lower limbs, the left being more affected than the right, with exaggerated knee and ankle jerks and bilateral extensor plantar reflexes.

Sensory system: There was analgesia below the junction of the upper and middle third of the right thigh and postural loss in the left great toe. Vibration was not felt below the costal margins.

Investigations.—X-rays of the cervical spine showed slight narrowing of the disc space C5–6 with arthritic changes due to disc lesion.

A cervical myelogram showed moderately large filling defects on the anterior aspect of the column of myodil opposite C5–6, C6–7.

Operation.—On 19.7.54 the cervical cord was explored and a protruding intervertebral disc was found between C5–6. Lesser protrusions were found between C6 and C7 and C4 and C5. The spinal cord was decompressed by the laminectomy and detached from the walls of the dorsal theca by divisions of the adjacent ligamentum denticulatum.

Three months after operation her condition had improved and she was able to walk without a stick and had less tingling in her legs and only occasional tingling in the arms.

One year after operation she showed further slight improvement, her gait was fairly steady though moderately spastic and she got only occasional pain in her neck. There was, however, very little change in her physical signs.

Comment.—In this case there is clear evidence of compression of the cervical spinal cord, yet a suspicion of disseminated sclerosis was aroused at the first examination. The mode of onset of the sensory disturbances and their spread till the patient felt numb from the waist down, are more characteristic of disseminated sclerosis than of myelopathy. So, too, are the precipitancy of micturition and the almost complete absence of the abdominal reflexes. The character and distribution of the sensory loss, which differed from the dysæsthesiæ, is more characteristic of extramedullary compression. This is probably a case of both disorders.

Case 16.—A. D., female, aged 53. Admitted London Hospital on four occasions: 10.3.54, 22.10.54, 4.5.55, 22.4.57. L.H. No. 9130/54.

History.—Four years ago she began to drag her right leg, and one month later she noticed that the left leg was also weak. About the same time she noticed a tingling feeling in her feet and right hand, and her right leg felt cold. She also had an occasional feeling of an electric shock running up her right leg.

P.H.—Seven years ago she started to have momentary attacks of unconsciousness in which she fell to the ground without warning, and was able to get up almost immediately.

Over the last four years she has been admitted to the London Hospital four times. She was first admitted in March 1954; her condition on examination was as follows:

Cranial nerves: Gross myopia of the right eye (−18 D). Slight myopia of the left. Divergent concomitant strabismus. Jaw-jerk not increased—other cranial nerves normal.

Motor system: Upper limbs—slight wasting of the right triceps and slight

generalized weakness of the right upper limb, the weakness being most marked in the following muscles—triceps, dorsiflexors of the wrist, extensors of fingers and small muscles of the hand. Power normal in left upper limb.

Lower limbs—spastic—moderate weakness of the right leg with severe spastic foot drop. Power normal in left lower limb. No ataxia.

No sensory loss.

Reflexes: Tendon-jerks all markedly exaggerated in upper and lower limbs, being brisker on the right than the left. Abdominal reflexes absent. Both plantars extensor.

All movements of neck limited. Gait spastic. Heart, chest and abdomen clear. B.P. 150/90.

Investigations.—X-ray cervical spine showed reduction of the disc between C5–6 with a little sclerosis and some osteophytosis.

Blood W.R. negative. EEG normal.

She was treated by rest in bed and later physiotherapy and her condition improved. After discharge she continued to attend out-patients. Her condition gradually deteriorated and at the time of her second admission in October 1954 she said that her legs felt a little heavier and that her right arm was weaker and stiffer.

On examination there was very little change in her physical signs. Once again she improved with physiotherapy and on discharge she was advised to wear a collar.

She came into hospital again six months later because her right hand had become weaker and clumsier and she was unable to write or knit.

On examination the weakness and spasticity of her limbs was more marked and she had some impairment of two point discrimination in her right hand.

A lumbar puncture done at this time showed *pressure* 170 *mm.* with *normal manometrics. Cells less than* 1 *per c.mm., protein* 20 *mg. per cent. Lange* 0010000. *W.R.* negative.

A myelogram showed a backward displacement of the column of myodil by a spondylotic bar at the C5–6 level (fig. 8, Plate LX).

Over the last two years her walking has become steadily worse and at the time of her last admission she could only walk twenty paces. She had also developed considerable emotional lability, having attacks of laughing and crying.

Six months ago her sight deteriorated and she had difficulty in reading. Bladder and bowel function were normal until six months ago, but since then she has had precipitancy and urgency of defæcation and micturition and has had occasional incontinence of urine. She had had no attacks of unconsciousness for three years.

Her last admission was in April 1957.

On examination at that time:

Cranial nerves: Severe degree of myopia of right eye and slight myopia in the left. Jaw-jerk exaggerated. Other cranial nerves normal.

Motor system: Marked spastic weakness of all limbs, more marked on the right than the left. Claw hand on right. Marked flexion and adduction of thumbs with other digits on grasping. Exaggerated plantar flexion of feet with inversion of right foot.

Reflexes: All exaggerated, those on the right being brisker than those on the left. Crossed adductor reflexes present. Abdominals absent. Plantars extensor.

Investigations.—Lumbar puncture: Pressure 140 mm. Normal manometrics. Cells 1 per c.mm. Protein 50 mg. per 100 ml.

X-ray of cervical spine: There is reduction in the disc spaces between the bodies of C5–6 and C6–7. Osteophytic protrusion is seen, particularly between the bodies of C5–6 on the right side. The reduction in disc spaces between the bodies of C6–7 with osteophytic formation was not so pronounced in 1954.

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Comment.—This patient suffered from akinetic epilepsy and progressive quadriplegia, attributed to disseminated sclerosis. She also had cervical spondylosis and over the three years during which she was under observation there was a marked change in the spondylotic changes in her cervical spine, and the c.s.f. protein had risen from 20 mg. per 100 ml. to 50 mg. per 100 ml.

Discussion

When cervical spondylosis and disseminated sclerosis are both present in the same patient there are three possible interpretations of their significance: (1) The symptoms of which the patient complains may be due to the disseminated sclerosis alone; (2) to the cervical spondylosis alone; or (3) both disorders may be contributing to the clinical picture.

(1) *Symptoms attributable to the disseminated sclerosis alone.*—In many cases no difficulty arises. A patient who presents the classical picture of disseminated sclerosis is found radiologically to have cervical spondylosis, but there is nothing in the clinical features to suggest that the cervical spondylosis has any responsibility for the symptoms. Sometimes the radiological changes of the cervical spondylosis are so slight that they are unlikely to be responsible for any interference with the spinal cord. When cervical spondylosis co-exists with disseminated sclerosis, which causes symptoms referable to the spinal cord alone, real diagnostic difficulty may arise. The clinical differentiation of the two is discussed below under (3).

(2) *The cervical spondylosis alone is responsible for the symptoms.*—When a patient is known to be suffering from disseminated sclerosis it is possible that the symptoms of which complaint is made are due entirely to an associated cervical spondylosis, and if this could be established it might offer the strongest case for surgical treatment. Nevertheless, if, as we shall suggest later, the effect of cervical spondylosis upon the spinal cord may be to make it more susceptible to the lesions of disseminated sclerosis at that level, it must often be impossible to distinguish the direct effect of cervical spondylosis upon the cord from its effect in focusing, as it were, the disseminated sclerosis.

(3) *Symptoms attributable to both cervical spondylosis and disseminated sclerosis.*—It is in this group that the greatest diagnostic difficulties are encountered. In practice the difficulty arises in one of two ways. The patient may present as an obvious case of disseminated sclerosis and the fact that the symptoms are also in part due to cervical spondylosis may not be obvious. On the other hand the presenting symptoms may be those of cervical spondylosis and the contribution made by the disseminated sclerosis may not be recognized. The former situation is likely to arise in the case of a patient who has already had symptoms of disseminated sclerosis as a result of lesions occurring above the level of the foramen magnum, for example, one or more attacks of retrobulbar

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neuritis or of diplopia. Paraplegia, or quadriplegia, arising at a later date and progressing insidiously in such a patient is very likely to be attributed solely to the disseminated sclerosis. The points which we have found useful as drawing attention to the cervical spine in such cases are a history of pain in the neck or of radicular pain in the upper limbs, the occurrence of muscular wasting and weakness in one or both upper limbs, especially if of segmental distribution, and, above all, diminution of one or more of the tendon reflexes in one or both upper limbs, especially the so-called inversion of the radial reflex. Such signs should lead to having the cervical spine X-rayed and it is usually possible to assess from the plain X-rays whether the changes are severe enough to cause compression of the spinal cord, though in doubtful cases myelography will be necessary.

When there is nothing in the patient's symptoms incompatible with a lesion of the spinal cord involving the cervical region, and radiography reveals cervical spondylosis, the suspicion of a co-existing disseminated sclerosis is unlikely to suggest itself unless either the colloidal gold curve in the cerebrospinal fluid is abnormal or the history or clinical examination reveals features unusual in cervical myelopathy due to spondylosis. The tempo of the development of symptoms is an important diagnostic point. The rapid onset of a sensory disturbance or of weakness involving one or both lower limbs, especially if subsequently followed by regression, is very suggestive of disseminated sclerosis. So are certain types of sensory disturbance, for example, an obtrusive numbness involving the whole of one or both lower limbs, and perhaps part of the trunk. In our experience, also, the early development of disturbances of bladder function is common in disseminated sclerosis and very uncommon in cervical myelopathy. In the latter condition, too, the abdominal reflexes are often relatively well preserved in spite of a fairly severe degree of paraplegia, in contrast with the common finding in disseminated sclerosis. A positive colloidal gold curve in the cerebrospinal fluid is, of course, of great value in confirming the presence of disseminated sclerosis, though its absence has not a corresponding negative significance.

Combined Spondylotic Myelopathy and Disseminated Sclerosis

Having discussed the difficulties in the way of arriving at the double diagnosis of myelopathy due to cervical spondylosis and disseminated sclerosis, we shall now describe how in our series of patients the two disorders appear to have influenced each other, and the problems of pathogenesis to which their association has given rise. In some cases it has been clear that the symptoms of the disseminated sclerosis have developed first and have later been exacerbated by the superimposed myelopathy due to the cervical spondylosis. This occurred, for example, in Cases 3, 4 and probably in 1 and 12. In such patients the clinical

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picture is usually a mixture of the symptoms and signs of the two disorders. Some of these can readily be attributed to the one or the other, though in the case of others, such as spastic paraplegia, it is impossible to distinguish the contribution made by each.

Other patients present a much more difficult problem. These are those in whom the disorder of function is limited to the spinal cord, cervical spondylosis has been shown to be present, and myelography has revealed a degree of compression of the cervical cord which is usually adequate to produce the symptoms of myelopathy. Yet such a patient may suffer also from disseminated sclerosis, and in the absence of a pleocytosis or an abnormal colloidal gold curve in the cerebrospinal fluid, the making of the second diagnosis can rest only upon an assessment of the history and the physical signs. It is important that such cases should be recognized because the appreciation of the co-existing disseminated sclerosis may influence a decision as to surgery, or explain why the results of surgery are not as good as might have been expected in an uncomplicated case of cervical myelopathy. In our Case 12 the correct diagnosis was rendered easy by the characteristic changes in the cerebrospinal fluid. Even if the fluid had been normal, however, the diagnosis of disseminated sclerosis would have been suggested by the long and fluctuating history, the tendency to become worse after febrile illnesses, and the early onset of urinary incontinence.

In our Case 15 the diagnosis of combined cervical myelopathy and disseminated sclerosis was made on the history and physical signs in the presence of a normal cerebrospinal fluid. This patient, whose first symptoms appeared three weeks after a fall downstairs, developed in the course of two years at the age of 41 a severe spastic paraplegia accompanied by dysæsthesiæ, first in the right lower limb and then in both, extending up to the trunk, and finally a burning girdle pain accompanied by itching at the level of the costal margin, a most unusual history in cervical spondylosis. After myelography had demonstrated cervical disc protrusions laminectomy was carried out and protrusions were found between C5–6 and, to a small extent, C6–7 and C4–5, but very little benefit followed operation.

The last two cases especially raise the interesting question whether the clinical picture of disseminated sclerosis is actually modified in its character or distribution by the supervention of compression of the cervical cord by disc protrusions, whether, in other words, the clinical picture resulting from the association of cervical spondylosis and disseminated sclerosis is ever more than a mere summation of the symptomatology of the two disorders. This is a question which can only be answered by a larger experience, but some light may be thrown on it by the observed effects of trauma upon patients suffering from both cervical spondylosis and disseminated sclerosis.

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The Effect of Trauma upon Patients Suffering from Both Cervical Spondylosis and Disseminated Sclerosis

We do not propose to discuss the general question of the relationship between trauma and disseminated sclerosis (*see* McAlpine and Compston, 1952; McAlpine, Compston and Lumsden, 1955). When the possible mode of action of trauma is entirely unknown its significance can be assessed only statistically. In cervical spondylosis, however, we are familiar with the fact that trauma to the head and neck can directly affect the cervical spinal cord. When a patient suffers from both cervical spondylosis and disseminated sclerosis we have a situation in which trauma may directly affect the nervous system in a patient suffering from the latter disease. In several patients in our series this occurred. Patient No. 3, eighteen years after the diagnosis of disseminated sclerosis was first made, while bending down to pick up a piece of wood developed a severe pain in his neck, radiating down both arms. He immediately experienced increased weakness in all his limbs and a progressive deterioration dated from that time. Patient No. 5 had twenty-eight years' history of disseminated sclerosis. A remission had lasted seven years when, at the age of 70, she fell and hit the back of her head. Six weeks later she developed numbness of the hands and increased weakness of the lower limbs. Certain points in this case are noteworthy. The fall on the back of the head presumably caused flexion of the neck and the maximal movement of the neck was shown by radiography to take place between C4 and C5 on flexion (figs. 3 and 4). The history, however, is not that characteristic of trauma to the cord in uncomplicated cervical spondylosis, in which the damage is apparent immediately after the injury. In this case the delay of six weeks suggests rather an exacerbation of the disseminated sclerosis. In Case 6 a fall off a ladder preceded the onset of the first symptoms by three months. In Case 8 the initial symptoms occurred a few weeks after a fall, and the exacerbation which brought her under observation developed a few days after a car accident which left her with a stiff and painful neck. The most striking instance was Case 7 who was already suffering from disseminated sclerosis, and, while undergoing cervical traction for spondylosis, developed retrobulbar neuritis in the left eye, trigeminal sensory loss on the left side, bilateral pyramidal signs and shortly afterwards retrobulbar neuritis in the right eye.

In two other cases, 9 and 15, falls not known to have affected the neck preceded by a short time the onset of symptoms. Thus in 7 of our 16 patients some trauma was closely related in time to the onset or an exacerbation of the disseminated sclerosis, and in 5 the trauma involved the neck. It is interesting to compare this incidence with that found by McAlpine, Compston and Lumsden (1955) in whose series of 250 cases, there was a history of trauma within three months of

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the onset in 36 (14 per cent) while in 22 of these 36 cases there appeared to be a correlation between the site of the injury and the site of the initial lesion.

Pathology and Pathogenesis

Two of the 17 patients in this series came to post-mortem and in both there was pathological evidence of the co-existence of disseminated sclerosis and cervical spondylosis. In 2 others, Nos. 13 and 15, the presence of cervical spondylosis was confirmed at operation. In both the cases in which a post-mortem examination was made, Cases 1 and 2, there were widely disseminated plaques of demyelination throughout the brain and spinal cord, the changes being very extensive in the cervical segments at the level where compression by the spondylotic bars had occurred. This may have been a chance finding, but it is more likely that the site of the demyelination was associated with the presence of the spondylotic bars. These bars may have caused interference with the blood supply of the cord or actual compression of the cord. It is quite likely that both these factors play a part.

The lesions in disseminated sclerosis are widely scattered throughout the central nervous system and because of this many writers have suggested that the blood vessels play an important part in determining the distribution of the lesions. In the acute forms and in severe terminal exacerbations of the disease some dilatation and engorgement of the vessels has been seen. Putnam and Adler (1947) believed that thrombosis of a small vessel may form the basis of a small plaque, but there is very little evidence to support this view. Dow and Berglund (1942), who examined 60 plaques from end to end, found evidence of thrombosis in only 9, and of these 2 were of doubtful authenticity and all were histologically recent. These authors considered that the thromboses were most likely due to the absorption of thromboplastic substances from neighbouring lesions. Lumsden (in McAlpine, Compston and Lumsden, 1955) suggests that while the veins and venules have some influence in determining the sites of origin of the plaques they do not influence the subsequent evolution or form of the plaque and that thrombosis, when it occurs, is a secondary process due to absorption of thromboplastic substances from the plaque. He further suggests that other hæmodynamic factors may operate by altering the permeability of vessel walls. Vasodilatation with slowing or even occasional stasis of the circulation leads to excessive transudation of fluid across the thin-walled veins. The mechanical effects of dilatation associated with reduced velocity of blood flow, might allow diffusion of larger molecules than in normal conditions and so antibodies or other substances could seep into the pericellular spaces permitting reactions on the surfaces of the medullated

fibres and oligodendrocytes. Cervical spondylosis could cause just such a mechanical effect as it has been shown that the spondylotic bars may cause compression of the cord (Brain *et al.*, 1952). If this occurs there must be partial obstruction of the thin-walled veins. The obstruction would at first be intermittent because the degree of compression of the cord is usually dependent upon the posture of the neck, in most cases extension causes the maximal deformity. Any heavy fall or forcible flexion or extension of the neck might further compress the cord. Relapse of the symptoms after trauma would seem to be due to further compression with consequent venous dilatation in a cord already damaged by demyelination. The initial lesion in disseminated sclerosis causes swelling and destruction of a variable number of the axis cylinders. Swelling of an axis cylinder depresses function until the swelling subsides.

Thus though function may recover, some degree of irreparable damage has persisted at the site of the plaque and this site is unduly vulnerable to further insults.

The Course and Treatment of the Combined Disorders

Cervical spondylosis is predominantly a disorder of the second half of life in which disseminated sclerosis tends to run a less acute and remittent and more steadily and slowly progressive course. The myelopathy caused by cervical spondylosis tends also to be insidious in its onset and, in the absence of trauma, slowly progressive. In 5 of our series of cases trauma in the neck appears to have either precipitated the first symptoms of, or substantially exacerbated, the disseminated sclerosis and the co-existence of the two disorders has tended to bring about a deterioration more rapid than would have been expected, had either been present alone. Laminectomy was carried out in 2 of our cases, 1 and 13, before the diagnosis of disseminated sclerosis was made. In one case, 15, this diagnosis was suspected, but it was thought that the element of uncertainty justified operation for the cervical spondylosis. In no case in which the diagnosis of disseminated sclerosis was certain did we feel justified in recommending laminectomy. Patients with disseminated sclerosis in general stand surgery badly and this series of cases illustrates the danger of trauma to the spinal cord in this disease. In any case the inevitably progressive course of disseminated sclerosis must render any possible benefit from operation transitory. It is indeed possible that some cases of unexplained rapid deterioration after laminectomy for cervical spondylosis occur in patients who also have unsuspected disseminated sclerosis. Immobilization of the neck in a collar seems a rational treatment, but in this series of patients has produced less benefit than in cervical spondylosis uncomplicated by disseminated sclerosis.

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Summary

(1) 17 patients who suffered from both cervical spondylosis and disseminated sclerosis are reported with two autopsies.

(2) Diagnostic difficulty may arise because the symptoms may be due (i) to the disseminated sclerosis alone, (ii) to the cervical spondylosis alone, or (iii) to a combination of the myelopathy caused by the spondylosis and disseminated sclerosis.

(3) Points of distinction between the two and the clinical features of the combined disorders are discussed.

(4) The effect of trauma especially to the neck is described.

(5) Pathology and pathogenesis are considered.

(6) The course and treatment of the combined disorders are discussed.

Acknowledgments

We are grateful to our neurosurgical and orthopædic colleagues at the London Hospital for allowing us to see their patients, to Dr. Michael Kremer for information about Case 5, and to Professor Dorothy Russell for her advice on the pathology of Cases 1 and 2. One of us (M. W.) has received a grant for this research from the Empire Rheumatism Council.

References

Dow, R., and Berglund, G. (1942) *Arch. Neurol. Psychiat.*, **47**, 1.

McAlpine, D., and Compston, N. (1952) *Quart. J. Med., N.S.*, **21**, 135.

——, ——, and Lumsden, C. E. (1955) "Multiple Sclerosis." Edinburgh and London.

Putnam, T. J., and Adler, A. (1947) *Arch. Neurol. Psychiat.*, **38**, 1.

Legends for Plates

Plate LVII

Fig. 1.—Sections of cervical spinal cord in Case 1, stained with Weigert-Pal.

Plate LVIII

Fig. 2.—Sections of cervical spinal cord in Case 2, stained with Weigert-Pal.

Plates LIX and LX

Figs. 3 and 4.—X-rays of cervical spine in Case 5 on flexion and extension, showing extensive spondylosis and forward movement of C4 on C5 on flexion.

Fig. 5.—X-ray of cervical spine in Case 2.

Figs. 6 and 7.—Myelograms in Case 13.

Fig. 8.—Myelogram in Case 16.

PLATE LVII

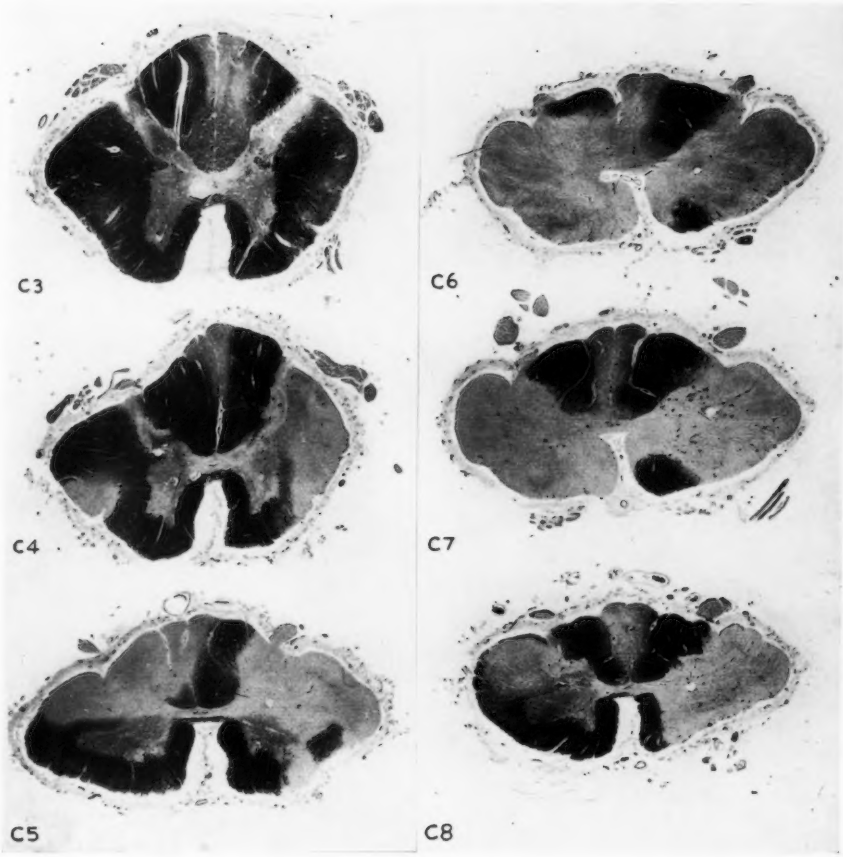

FIG. 1.

To illustrate article by Russell Brain and Marcia Wilkinson.

PLATE LVIII

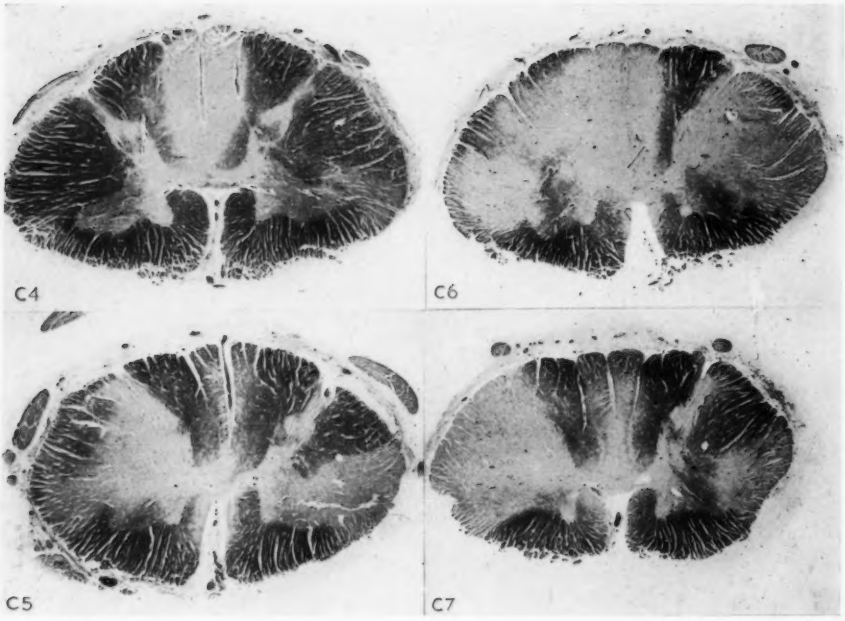

FIG. 2.

To illustrate article by Russell Brain and Marcia Wilkinson.

PLATE LIX

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 6.

To illustrate article by Russell Brain and Marcia Wilkinson.

PLATE LX

FIG. 7.

FIG. 8.

To illustrate article by Russell Brain and Marcia Wilkinson.

THE APPEARANCE OF THE AQUEDUCT AND ITS RELATIONSHIP TO HYDROCEPHALUS IN THE ARNOLD-CHIARI MALFORMATION

BY

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THE cause of hydrocephalus in the Arnold-Chiari malformation is still unknown though certain views have been expressed notably those of Russell and Donald (1935) and Lichtenstein (1942; 1955). Russell and Donald believe that the cerebrospinal fluid (C.S.F.) escapes normally from the fourth ventricle but is prevented from passing upwards by the cerebellar "tongue" impacted in the foramen magnum. Lichenstein considers that there is tethering of the lower end of the cord at the site of the spina bifida and that this exerts traction on the brain-stem. This traction causes stenosis of the aqueduct with resultant hydrocephalus.

Verbiest (1953) examined 11 cases of the Arnold-Chiari malformation by air ventriculography and came to the conclusion that the hydrocephalus is not readily explicable by any one of the generally accepted mechanisms.

Potter (1952) also expresses a doubt as to the normality of the aqueduct in some cases though she upholds Russell and Donald's theory.

It was accordingly decided to examine the aqueduct in a series of cases of the Arnold-Chiari malformation.

The earliest full descriptions of this condition were given by Chiari (1895) and Solovtzoff (1901) though it had been previously noted by Arnold (1894). Schwalbe and Gredig (1907) described further cases and termed the lesion the Arnold-Chiari malformation. The condition has been described since by numerous authors and it serves here to mention only the salient features. These comprise: elongation of the lower brain-stem; a dorsal tongue of cerebellar tissue displaced below the foramen magnum, overlying and adherent to the posterior surface of the medulla and usually continued caudally on to the posterior surface of the cervical cord; between these two components an elongated slit-like fourth ventricle. The roof foramina also lie below the foramen magnum. The medulla is not infrequently angled backwards and downwards in relation to the upper cervical cord. The upper cervical nerve

roots pass in a horizontal or upward direction to reach their respective spinal foramina. A severe degree of spina bifida is invariably present.

Material and method.—The material was obtained from the routine pædiatric autopsy service in this region.

(1) *Controls.*—20 normal brains from fœtuses, neo-nates and infants ranging from 28 weeks gestation to 10 weeks old, dying from conditions unrelated to disease of the nervous system, were examined. In 4 of these the whole mid-brain was sectioned serially. The remaining 16 were examined in a similar manner to the Arnold-Chiari cases macroscopically (v.i.) but only 4 of these were also examined microscopically.

(2) *Arnold-Chiari cases.*—20 brains were examined; these were unselected except that severely macerated fœtuses and those subjected to craniotomy to facilitate delivery were excluded. The brain and spinal cord were exposed by a dorsal approach and then removed in continuity and fixed in 15 per cent aqueous formalin. All cases had a severe degree of spina bifida, either a meningomyelocele or a myelocele.

After hardening, the mid-brain was isolated and several transverse slices made at different levels in all cases except the fourth (v.i.). If the aqueduct was obviously and adequately patent throughout, only one or two blocks were processed and a single section from each examined. If the aqueduct was not seen or appeared unusually narrow the relevant blocks were serially sectioned.

All blocks were embedded in paraffin wax and sections cut at 6μ and stained with hæmatoxylin and eosin. From the blocks cut serially every 20th section was mounted for microscopic study.

Measurement.—By means of a calibrated 0·5 mm. squared grid inserted into the eyepiece of a microscope the cross-sectional area of the lumen of the aqueduct was measured at any given level in terms of small squares. The result was then converted into sq. mm.

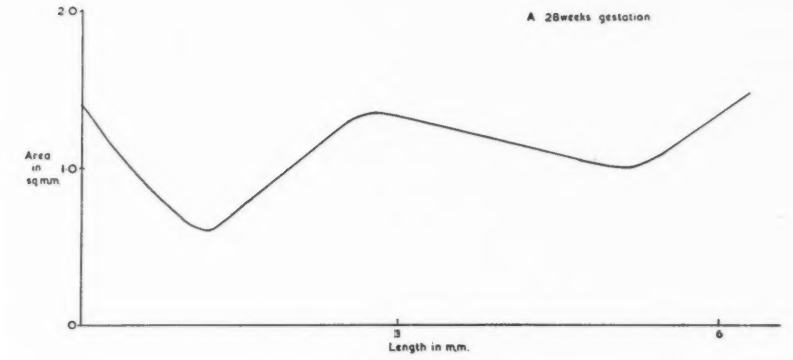
Results

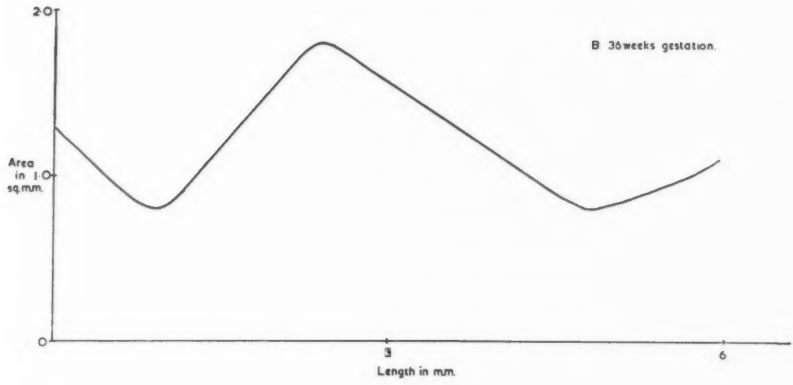
The Normal Aqueduct

(A) *Size and shape.*—The cross sectional areas of the aqueducts from the 4 normal brains examined in their entirety by serial section are shown graphically in fig. 1. Their ages were as follows: 28, 36 and 40 weeks gestation, and 10 weeks old.

The pattern of these graphs demonstrates that the aqueduct is constricted at two levels. These constrictions are located at horizontal levels passing through the middle of the superior colliculus and the intercollicular sulcus respectively and this configuration corresponds closely with that described by Woollam and Millen (1953) as occurring in adults.

In our series the lumen of the aqueduct varies at the upper constriction from 0·4 to 0·8 sq. mm. and at the lower from 0·5 to 1·0 sq. mm.


A 28weeks gestation
2·0
Area in sq.mm.
1·0
0
3
6
Length in mm.


B 36weeks gestation.
2·0
Area in sq.mm.
1·0
0
3
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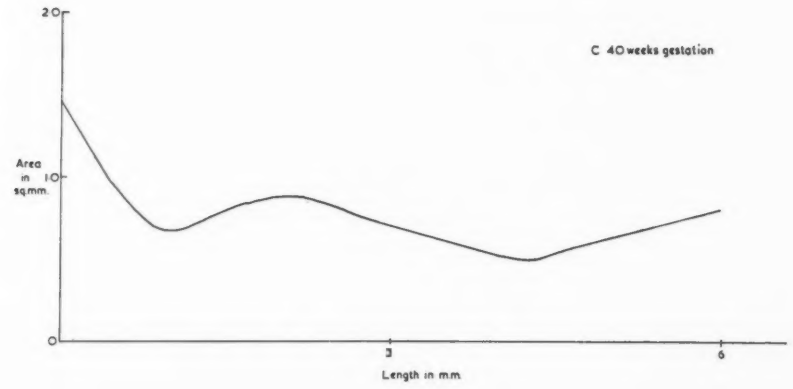
Length in mm.


C 40weeks gestation
2·0
Area in sq.mm.
1·0
0
3
6
Length in mm.

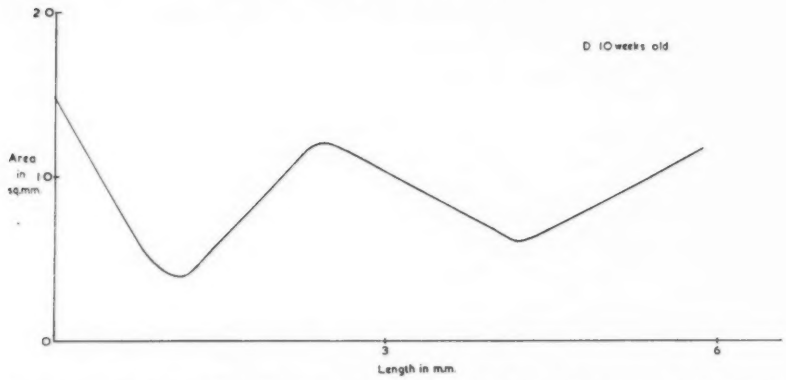


FIG. 1.—A. B. C. D. Graphs showing cross-sectional area of aqueduct at different levels in 4 normal controls (*see previous page*).

This series is too small to determine the significance of age on the size of the lumen, but it may be noted that the 10-week-old infant brain shows the narrowest constriction. Moreover some of Woollam and Millen's adult cases had even narrower constrictions (upper, ranging from 0·2 to 1·8 sq. mm.; lower, from 0·4 to 1·5 sq. mm.). But the validity of these comparisons must remain in doubt for no allowance can be made for differing shrinkage factors in the two series. Nevertheless it would appear that when brain size is taken into account the fœtal aqueduct is relatively wider at the sites of constriction than the adult aqueduct. It is of interest to note that Bickers and Adams (1949) report that the lumen of the aqueduct is greater in the third month of fœtal life than at birth.

The additional 4 normal controls examined microscopically, but not serially, were selected because in each the aqueduct seemed narrower over some portion of its length than in any of the remaining 12 controls. The cross-sectional area of the aqueduct in each of these 4 cases at the level examined is given in Table I.

TABLE I

	Age	*Cross-sectional area of aqueduct*
(1) A.129/56.	24 weeks gestation	0·3 sq. mm.
(2) A.128/56.	32 weeks gestation	0·3 sq. mm.
(3) A.131/56.	27 weeks gestation	0·4 sq. mm.
(4) A.110/56.	32 weeks gestation	0·8 sq. mm.

Thus in the 8 cases examined microscopically in whole or in part the lumen of the aqueduct never fell below 0·3 sq. mm. Fig. 2, Plate LXI, illustrates the appearances of the aqueduct at different levels in one of these cases.

(B) *Presence of subsidiary channels.*—In several aqueducts which

otherwise looked normal as regards size and shape the presence of one or more subsidiary ependymal lined channels was noted. These appeared as small out-pouchings occasionally from the lateral or dorsal walls lying close to the aqueduct but more constantly in the median plane ventral to the main channel. A ventrally situated subsidiary channel was found in all 4 control aqueducts serially sectioned.

The term simple forking is here employed to describe the presence of this ventral channel which commences as a diverticulum from the aqueduct usually near the lower constriction. The subsidiary channel is directed cephalad, ends blindly and is only a few hundred μ in length. Its upper end often lies at some distance from the main channel and is separated from it by normal nervous tissue (fig. 3, Plate LXII).

In no instance does this subsidiary channel communicate either with the third or fourth ventricles. Russell (1949) noted this simple type of forking in two non-hydrocephalic subjects dying from causes unrelated to disease of the nervous system.

The Aqueduct in the Arnold-Chiari Malformation

Histological study revealed that in the present series the aqueduct showed one of the following: (1) a developmental abnormality; (2) dilatation; (3) no apparent abnormality. For convenience the cases have been grouped in this order and details are given in Table II.

(1) *Developmental Abnormality.*—10 out of the 20 cases were considered to have some degree of maldevelopment of the aqueduct—other than simple forking—of such a degree as to impede the normal flow of C.S.F.

These abnormalities fell into the categories of "forking" and stenosis as described by Russell. To avoid confusion with the condition of simple forking already described, which may occur in normal non-hydrocephalic brains we propose to use the term complex forking in the sense that "forking of the aqueduct" was used by Russell.

Complex forking is a condition of the aqueduct in which for part of its course two distinct channels are present in the mid-sagittal plane separated from one another by normal nervous tissue. The ependyma is normal and there is no gliosis. But unlike simple forking, the dorsal channel narrows considerably, branches, and becomes broken up into two or more small ependymal lined channels surrounded by groups of displaced ependymal cells amongst which further small tubules may be seen. In the present series of cases the dorsal channel became reconstituted and entered the fourth ventricle. The ventral channel, as in the simple variety of forking, is directed cephalad and ends blindly. It would appear that the branching and breaking up of the dorsal channel is the salient feature of this anomaly and is responsible for the inadequate

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TABLE II.—DETAILS OF THE 20 CASES OF THE ARNOLD-CHIARI MALFORMATION

Case No.	*Age*	*Gestation*	*Weight in grammes*	*Degree of hydrocephalus*	*Degree of involvement of occipital horns*	*Macroscopical appearance of aqueduct*	*Microscopical appearance of aqueduct*
1 (OA51/56)	S.B.	32 weeks	1,900	++	++	Not visible	Complex forking
2 (OA176/54)	S.B.	Less than 28 weeks	716	+++	n.o.	Not visible	Complex forking
3 (NPA265/55)	5 hours	—	3,230	+++	n.o.	Not visible	Complex forking
4 (OA97/54)	7 weeks	—	2,950	+++	n.o.	No channel could be seen in lower third of mid brain	Forking but examination incomplete
5 (NPA27/55)	10 days	—	2,730	+++	n.o.	Extremely small	Stenosis
6 (OA55/56)	S.B.	36 weeks	2,420	++	n.o.	Extremely small slit	Stenosis
7 (RHSC) (95/55)	11 days	—	3,840	+++	+++	Narrow slit, just visible	Stenosis
8 (OA118/54)	1 day	—	4,100	+++	n.o.	Very small	Stenosis
9 (RHSC4/56)	5 weeks	—	2,520	+	+	Very small	Stenosis
10							

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10 (SMP8/56)	3 days	—	1,680	++	n.o.	Not visible in lower two-thirds of mid-brain	Stenosis
11 (NPA181/55)	4 weeks	—	2,660	+++	n.o.	Dilated	Dilated
12 (NPA155/54)	3 days	—	3,300	++	n.o.	Normal	Normal
13 (NPA162/54)	9 days	—	3,100	+++	no..	Normal	Normal
14 (NPA172/54)	5 days	—	2,866	+	n.o.	Normal	Normal
15 (NPA174/54)	5 weeks	—	1,820	+	+++	Normal	Normal
16 (OA162/54)	S.B.	40 weeks	3,140	+++	n.o.	Normal	Normal
17 (NPA258/55)	2½ days	—	3,310	+++	+++	Normal	Normal
18 (OA275/55)	S.B.	Less than 28 weeks	780	+	+	Normal	Normal
19 (OA278/55)	5 weeks	—	2,580	++	+++	Normal	Normal
20 (SMP246/55)	S.B.	36 weeks	2,640	+	n.o.	Normal	Normal

Note: S.B. = Still birth. *Degrees of Hydrocephalus:* + = Mild. ++ = Moderate. +++ = Severe. *n.o.* = no observation made.

C.S.F. circulation, for the ventral channel was always exceedingly narrow and was never found to communicate with both ventricles.

Cases 1, 2 and 3 were examples of complex forking.

In Cases 1 (OA51/56, fig. 4), and 2 (OA176/54), the microscopical findings were similar. The aqueduct which was readily traced caudally from the third ventricle became very small and irregular eventually breaking up into several small channels At a lower level a new ventrally situated channel appeared in the mid-line; this gradually moved dorsally to join the largest of the posterior groups of channels which then continued into the fourth ventricle.

In Case 3 (A265/55), the aqueduct followed a similar pattern to that described above but showed also a dorsal fork. Both dorsal and ventral forks were directed cephalad.

Even without calibration it was apparent that in none of these cases was there an adequate channel for the passage of C.S.F. Neither peri- nor intra-aqueductal gliosis was seen.

Case 4 (OA97/54). This mid-brain was divided in a parasagittal plane and the portion containing the aqueduct sectioned horizontally. Macroscopically the aqueduct was not seen in its lower part and microscopically in the one available block two distinct channels were noted, one dorsal, the other ventral, lined by normal ependyma; there was no gliosis. No measurements were made. This case was obviously an example of forking but whether of the simple or complex type was uncertain as the method of examination did not allow a conclusive study to be made and complete serial sections were not possible.

Cases 5–10 showed stenosis of the aqueduct. By stenosis is meant a condition in which the aqueduct in at least a part of its course is abnormally small. The ependymal lining however is quite healthy and there is no associated intra- or peri-aqueductal gliosis. The aqueduct usually assumes an abnormal shape. What in effect constitutes stenosis of the aqueduct is difficult to define in the absence of accepted standards of normality in the age group with which this paper deals. In the series of normal controls the minimum aqueductal cross sectional area was 0·3 sq. mm.

Cases 5 (A27/55, fig. 5), 6 (OA56/56), 7 (RHSC95/55), 8 (OA118/54), 9 (RHSC4/56) and 10 (SMP8/56, fig. 6) were all believed to be examples of stenosis.

In all these cases the aqueduct macroscopically appeared very small and was often barely perceptible.

Microscopically the first five of these cases were similar in that the aqueduct showed an abnormal configuration being elongated in the antero-posterior plane and narrowed from side to side. Over some part of its course each aqueduct had a smaller calibre as estimated by

direct measurement than was ever encountered in the controls. The narrowest cross section area in each case respectively was 0·2 sq. mm.

Case 10 (fig. 6) was an extreme example of stenosis differing in two respects from the remainder in this group. The aqueduct which narrowed considerably in its middle-third became T-shaped and then cruciate. There was virtually no lumen as the ependymal lining was in partial apposition. At a lower level a small ventral fork appeared. The presence of the latter plus the configuration of the main posterior channel which seemed to be on the point of breaking up into numerous minute ependymal lined canals, but in fact never did so, made classification difficult. These appearances could have been interpreted as complex forking but the case was eventually considered to be an example of simple forking with stenosis of the dorsal channel.

(2) *Dilatation.*—The aqueduct in Case 11 (NPA181/55), was grossly dilated macroscopically. The infant was born several weeks prematurely and lived one month. The entire ventricular system including the fourth ventricle was dilated but there was also an acute meningitis and purulent ventriculitis.

(3) *No apparent abnormality.*—In the remaining 9 cases the aqueduct appeared normal macroscopically and in the random microscopical sections examined the cross-sectional area fell within the limits of the normal controls.

Hydrocephalus

Reference to Table II shows that ventricular dilatation was present in all cases though its degree and the size of the head were variable. In several of the stillbirths and those infants surviving for only a short time the head was often not enlarged yet section of the brain revealed a severe hydrocephalus. The occipital horns frequently showed disproportionate dilatation in comparison to the other compartments of the lateral ventricles; this was considered to be partly compensatory in nature owing to the reduction in size of the cerebellum which is a common feature of the Arnold-Chiari malformation. Dilatation of the third ventricle was never striking. In only one case (Case 11) was the fourth ventricle dilated but there was an associated basal meningitis.

Other Malformations

Though this study was concerned with the aqueduct in the Arnold-Chiari malformation it was early recognized that the hind-brain deformity was accompanied either constantly or sporadically by several other malformations of both the central nervous and skeletal systems. Cameron (1957*a*; *b*) has described many of these in detail. Craniolacunia and reduction in the size of the posterior cranial fossa were almost constant findings. The former deformity was variable in degree.

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Various abnormalities of the cervical vertebræ were also encountered in several cases. In all there was a remarkable increase in the number and size of the vascular channels, mainly venous, of the leptomeninges overlying the Arnold-Chiari malformation and in about half the cases this excessive vascularity was also present over the cerebrum. Large and abnormally situated venous channels were occasionally seen within the brain substance particularly in the mid-brain. Microgyria was observed in about two-thirds of the cases. Solitary examples of hydromyelia and diastematomyelia were encountered.

Since this series was completed examination of further examples of the Arnold-Chiari malformation has revealed in two instances fusion of the posterior parts of the thalami. This condition has already been described by Cameron (1957*a*), as enlargement of the massa intermedia. He states that it may form one of a triad of associated malformations, the other two being hypoplasia of the falx cerebri and partial obliteration of the great longitudinal cerebral fissure. In retrospect we consider that our failure to note significant dilatation of the third ventricle may be explained by the presence of this thalamic abnormality in a high percentage of our cases.

Discussion

The results show that of 20 cases of the Arnold-Chiari malformation, 9 showed either complex forking or stenosis of the aqueduct. In a further case the lower end of the aqueduct could not be identified macroscopically and microscopically forking was evident, but whether of the simple or complex type was not determined. Nevertheless hydrocephalus was present in all cases and its degree did not appear to be related to the presence of severity or the aqueductal lesion.

Cameron (1957*a*) found that the aqueduct was abnormally narrow in 13 out of 26 cases of severe spina bifida, 24 of which also showed the Arnold-Chiari malformation. In 10 of these, however, the narrowing was considered to be due to post-inflammatory stenosis and in only 3 to developmental defects alone. Post-inflammatory stenosis appears to be a similar condition to gliosis of the aqueduct which Russell has described in detail and differentiated from stenosis and forking. There were no examples of this type of lesion in our series and this may be explained by the fact that the longest survival was only seven weeks, and the majority of live births died within a few days. Therefore, though many of these cases had an ascending infection of the central nervous system, there had probably been insufficient time for aqueductal gliosis to develop.

Lichtenstein drew attention to the occurrence of stenosis of the aqueduct in the Arnold-Chiari malformation and he attributed this to downward traction on the mid-brain by the tethering of the spinal cord

at the site of the spina bifida. He noted that the aqueduct was narrowed from side to side and elongated in the antero-posterior plane. While it it is true that a similar appearance was noted in cases 5–9, of the present series, nevertheless in none was there evidence of distortion or compression of the periaqueductal grey matter which one might expect if the abnormal shape of the aqueduct resulted merely from mechanical displacement. Moreover cases 1, 2 and 3 showed complex forking which can only be considered a developmental abnormality and case 10 showed both forking and narrowing of the dorsal channel. For these reasons we believe that all the aqueductal abnormalities noted in this series were developmental in origin and consisted of an exaggerated or abnormal degree of closure of the neural tube at this level.

By contrast the spina bifida, which was constantly present, is known to be due to a failure of closure of the neural tube. Thus it is possible to consider that both the lesions of the aqueduct and the cord result from a disturbance of closure of the neural tube.

Returning to a consideration of the hydrocephalus it is only too apparent that its ætiology in every case of the Arnold-Chiari malformation is still far from being understood. For although half of our cases had aqueductal lesions of sufficient severity to account for the occurrence of hydrocephalus if found alone in otherwise normal brains, in the remainder no aqueductal abnormality could be detected. In those with an apparently normal aqueduct the obstruction to the flow of C.S.F. may have occurred at lower levels as had been suggested by other authors—(1) mechanical obstruction of the foramina in the roof of the fourth ventricle by the squeezing of the medulla and cerebellar tongue into the cervical canal (Ingraham and Scott, 1943); (2) the C.S.F. may escape normally from the fourth ventricle but is prevented from passing cephalad by the cerebellar tongue impacted in the foramen magnum (Russell and Donald); (3) the basal cisterns may be obstructed by an aseptic meningitis (Ingraham and Scott).

If the obstruction is at the lower end of the fourth ventricle or in the basal cisterns it would be expected that the fourth ventricle and aqueduct should share in the ventricular dilatation. Such a dilatation was encountered in only one case (Case 11) and this was complicated by severe infection.

It may be that there is a relative disproportion between the posterior fossa and its contents which produces a generalized compression of the brain-stem and cerebellum with resultant narrowing of the whole of the hind-end of the ventricular system.

We agree with Verbiest that there is no simple or constant explanation for the hydrocephalus and that obstruction to the flow of C.S.F. may occur at various levels; but we believe that the high incidence of aqueductal abnormalities is a significant factor and must be taken into consideration

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before any operative procedures are planned or undertaken to relieve the hydrocephalus.

SUMMARY

(1) The aqueduct was examined in 20 cases of the Arnold-Chiari malformation and contrasted with 20 normal controls from a similar age group.

(2) 4 control aqueducts were serially sectioned, measurements carried out by means of a calibrated eyepiece and graphs constructed of the cross sectional area at different levels.

(3) The configuration of the aqueducts in young brains was found to correspond closely with that previously described in adults.

(4) 50 per cent of the cases with an Arnold-Chiari malformation showed an aqueductal abnormality, considered to be developmental.

(5) Two forms of forking of the aqueduct were distinguished.

(i) Simple forking, occurring in otherwise normal brains and having no pathological significance.

(ii) Complex forking, the distinctive feature of which is the break up and disorganization of the dorsal channel. This form is associated with hydrocephalus.

(6) The cause of the hydrocephalus, present in all cases, was discussed.

10 cases showed an aqueductal abnormality of sufficient degree to explain the hydrocephalus.

In 9 cases generalized compression of the hind-end of the ventricular system was considered a possible explanation.

One case with ventriculitis and meningitis had dilatation of all ventricles and this was thought to be due to meningeal obstruction of the roof foramina or the basal cisterns.

We wish to thank Professor G. L. Montgomery, Drs. A. R. Macgregor and A. E. le Roux for advice and criticism, and the technical staffs of the Pathology Department of the Royal Hospital for Sick Children and the Neuropathology Department, Edinburgh, for the preparation of the material. We are indebted to the Photomicrography Department of the University of Edinburgh for the illustrations.

REFERENCES

ARNOLD, J. (1894) *Beitr. path. Anat.*, **16**, 1.

BICKERS, D. S., and ADAMS, R. D. (1949) *Brain*, **72**, 246.

CAMERON, A. H. (1957*a*) *J. Path. Bact.*, **73**, 195.

—— (1957*a*) *J. Path. Bact.*, **73**, 213.

CHIARI, H. (1895) *Denkschr. Akad. Wiss. Wien.*, **63**, 71. Quoted by Schwalbe and Gredig.

INGRAHAM, F. D., and SCOTT, H. W., Jr. (1943) *New Engl. J. Med.*, **229**, 108.

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FIG. 2A.

FIG. 2B.

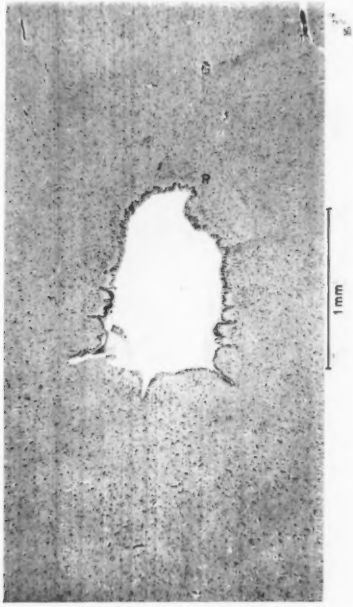

FIG. 2C.

To illustrate article by A. MacFarlane and A. F. J. Maloney.

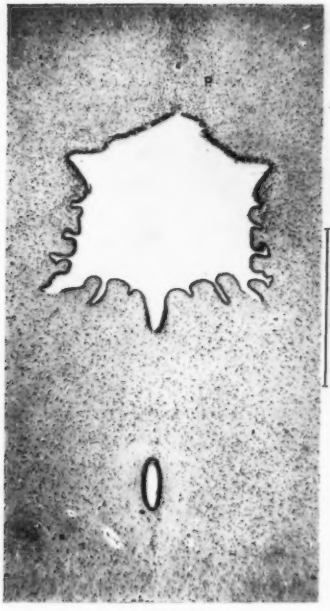

FIG. 3.

FIG. 4.

FIG. 5.

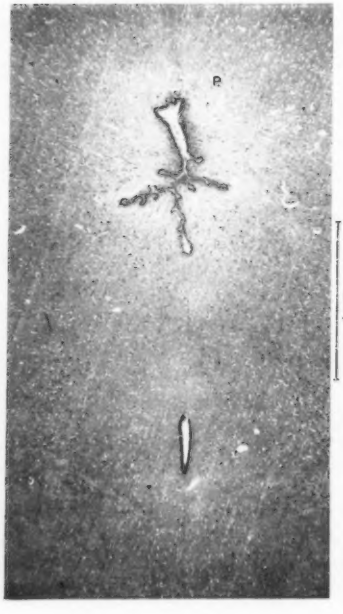

FIG. 6.

To illustrate article by A, MacFarlane and A. F. J. Maloney.

LICHTENSTEIN, B. W. (1942) *Arch. Neurol. Psychiat., Chicago*, **47**, 195.
—— (1955) *Trans. Amer. Neurol. Ass.*, **80**, 50.
POTTER, E. L. (1952) Pathology of the Fœtus and the Newborn, Chicago, p. 426.
RUSSELL, D. S. (1949) Observations on the Pathology of Hydrocephalus, *Spec. Rep. Ser. med. Res. Coun.*, No. 265, London.
——, and DONALD, C. (1935) *Brain*, **58**, 203.
SCHWALBE, E., and GREDIG, M. (1907) *Beitr. path. Anat.*, **40**, 132.
SOLOVTZOFF, N. (1901) *Nouv. Iconogr. Salpet.*, **14**, 118 and 251.
VERBIEST, H. (1953) *J. Neurol. Neurosurg. Psychiat.*, **16**, 227.
WOOLLAM, D. H. M., and MILLEN, J. W. (1953) *Brain*, **76**, 104.

LEGENDS FOR PLATES

PLATE LXI

FIG. 2.—Normal aqueduct at 3 levels in infant 10 weeks old.

(*a*) upper constriction H. & E. × 40.
(*b*) ampulla H. & E. × 40.
(*c*) lower constriction H. & E. × 40.

PLATE LXII

FIG. 3.—Simple forking in normal control. Note small ventral channel.

FIG. 4 (*Case* 1).—Complex Forking. H. & E. × 40.

FIG. 5 (*Case* 5).—Stenosis. H. & E. × 40.

FIG. 6 (*Case* 10).—Shows features of simple forking with stenosis of dorsal channel. H. & E. × 40.

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INTRACRANIAL BRUITS IN HEALTH AND DISEASE

BY

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THE first observations of cephalic bruits were reported about 120 years ago in the publications of Fisher (1834 and 1838). This writer described bruits in various conditions—hydrocephalus, dentition, meningitis, cerebral inflammations, and interestingly enough in an elderly patient of 73 who succumbed to a cerebral hæmorrhage. He suggested that the bruits were originating in the basal arteries and he compressed the carotid arteries, noting that the bruits diminished. All but 2 of his patients were children.

Whitney (1843) noted bruits in 189 out of 225 children with protracted dentition and he agreed with Fisher in thinking that the bruits were due to compression of the basal vessels passing through the skull base and congested brain. Wirthgen (1855) listened to the heads of 52 children under the age of 4 years and found a bruit present in 22 cases. Both he and Hennig (1856) went so far as to suggest that the absence of a bruit might be an indication of incipient or active disease. Henoch (1861) found the cranial bruits much more frequently (24 of 33 cases) in rachitic children with delayed fontanelle closure and agreed with earlier writers that the bruits were very much more frequent when the fontanelle was open, but pointed out that sometimes a bruit might be heard in other parts of the skull even when the fontanelle was closed.

Osler (1880) described several cases of bruit in children after fontanelle closure and examined a further 60 children under 3 years, finding bruits in 8 of them. He mentioned the work of James Bell who found a 6 per cent incidence of bruits in 100 young children.

Roger (1883) suggested that a patent fontanelle or faulty union was necessary to the transmission of the usual cephalic bruit—but he mentioned two older children aged 13 and 14 years with bruits, which he ascribed to other causes. He considered the "Souffle Cephalique" to be due to anæmia.

At the turn of the century with the rapid development of neurosurgery

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more concrete correlations of bruits have been made. Beadles (1907) describes bruits in 2 cases of intracranial aneurysm from a series of 555. Cushing (1928) records bruits in vascular anomalies. Still (1921) found bruits much more frequent under the age of 4 than over, finding only 4 bruits in 93 children between 4–16 years.

More recently Hamburger (1931), Sears (1938) and Mackenzie (1955) have written detailed accounts of bruits in disease, with special reference to their pathological significance.

Dalsgaard-Nielsen (1939) gives his results of cephalic auscultation in some 2,000 individuals. He was unable to find a bruit in any healthy individual over the age of 2½ years. Up to this age he found a maximum incidence of bruits of 19 per cent in the 12–18-month-old infants. It is worth noting here that his technique of auscultation was different from ours, which fact may well account for the gross disparity in our findings, as will be seen later. Finally the situation has been fully reviewed by Dodge (1956) who points out that there are no reliable figures to show the frequency of bruits in children.

In this communication we wish to review the incidence of cephalic bruits in apparently healthy individuals and to this end have personally examined over 700 persons between the ages of 4 and 70.

These figures are contrasted with the findings on auscultation in a diversity of diseases both neurological and general systemic.

Technique of auscultation.—Standard diaphragm and bell stethoscopes were used. Six "standard" listening points on the skull were used. These were over the globes, the temporal fossæ and the retro-auricular or mastoid regions. In addition carotid and manubrial points were employed to exclude conduction of cardiac bruits. The standard listening points were used first "at rest" and second with unilateral carotid compression. Thus each listening point was covered three times in each patient. It should be further stated that auscultation of these patients was carried out either in the erect or sitting position. Special attention was not paid to pulse rates, but naturally amongst the children there were some who were a little apprehensive and therefore had tachycardia.

Incidence of Bruits in Health

In using the technique described above for eliciting intracranial bruits it became clear that there were two sorts of bruits. First, those occurring spontaneously and secondly, those heard only on contralateral carotid compression. In the description and discussion we have therefore called them spontaneous and evoked bruits. We want to stress that, apart from this, the qualities of the bruits were similar. The spontaneous bruits were as a rule augmented by contralateral carotid compression and abolished or greatly reduced by homolateral carotid compression.

Most studies of cephalic bruits in healthy individuals have been made

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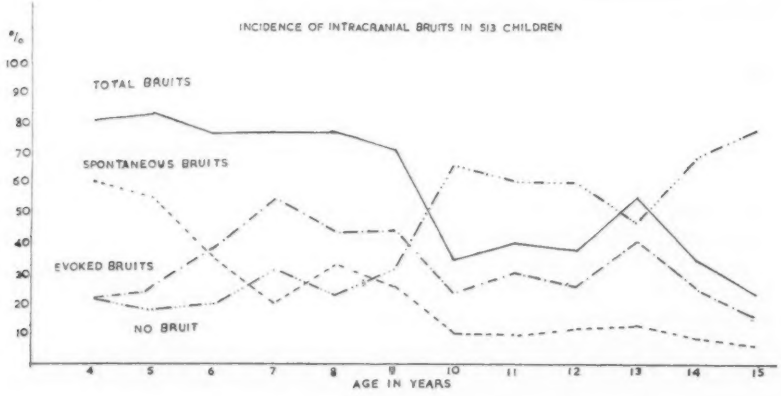
in infants and children. In the present report, therefore, the results will be presented in the first instance in two portions: A, children, B, adults. Subsequently the two will be considered as a whole.

A. *Children.*—513 children from the ages of 4–15½ were examined by one of us (G. M.) at the Pentrepoeth School, Carmarthen. Reference to Table I and the associated graph shows that spontaneous bruits occur in up to 60 per cent of 4–5 year olds and that this figure drops to 20 per cent in the 7 year olds. A further sharp fall occurs in the 10th year to 10 per cent. Therefore there is a slow fall to 4 per cent at 15–16 years of age.

These figures are paralleled at a higher level for evoked bruits (i.e. bruits brought out by unilateral carotid compression). Reference to Table I and the associated graph shows that the evoked bruits are always more frequent than spontaneous bruits, except in the very young. On the whole, evoked bruits occur more than twice as frequently as the spontaneous. In this series at the age of 15½ the evoked bruits occurred in 18 per cent of the children.

TABLE I.

SPONTANEOUS BRUITS			EVOKED BRUITS		
RIGHT	BILATERAL	LEFT	RIGHT	BILATERAL	LEFT
31	44	21	47	91	31
98			169		



In Table I and attached graph it will be seen that the total bruits, i.e. the sum of evoked and spontaneous was about 70 per cent until the age of 9–10 years, at which time a profound drop occurs to 35 per cent. There is then a slow build-up to the age of 13 and a subsequent fall to 22 per cent. This table and graph also show the rise in the "silent" children, 9–10 years of age is again crucial and the rate rises to 78 per cent by the age of 15.

Further breakdown of the figures into sex incidence reveals no significant difference. In terms of lateralization of the bruits, reference to Table II

TABLE II.

YEARS OF AGE	TOTAL CASES	TOTAL BRUITS	EVOKED BRUITS	SPONTANEOUS BRUITS
4— 5	27	22	7	15
5— 6	49	37	19	18
6— 7	40	30	22	10
7— 8	28	21	12	9
8— 9	56	39	25	14
9—10	38	14	9	4
10—11	40	16	12	4
11—12	46	18	12	6
12—13	66	35	26	9
13—14	75	25	19	6
14—15	48	11	8	3
TOTAL	513	267	169	98

shows that the majority were audible on both sides of the skull, with roughly equal numbers lateralized right and left. Evoked bruits show the same features. These findings argue against there being any significant number of underlying pathological causes in the evoked groups.

As regards conduction of carotid or cardiac bruits, there were 15 cases with chest or neck bruits. Of these 7 were associated with intracranial bruits. 3 of these were audible in the posterior fossa. It was not thought that the remaining 4 bruits were due to conduction from the neck since they behaved on carotid compression in exactly the same way as the spontaneous bruits.

In view of the remarkable frequency of bruits in these children we thought it would be of interest to see if there was any evidence of familial incidence. Accordingly, the twin children were noted and 6 sets were

TABLE III.

BRUITS IN TWINS

TWIN NO.	SEX OF TWINS		SPONTANEOUS BRUITS		EVOKED BRUITS		AGE
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	
1	1	1	0	0	1	1	6
2	1	1	0	0	1	1	6
3		2*		1		1	13
4		2		1			13
5	2*		0		0		14
6	1	1	0	0	1	0	10
TOTAL	5	7	0	2	3	3	

* TWIN NO. 3 AND 5 ARE IDENTICAL PAIRS

found. Table III shows the bruit pattern obtained. In this group there were 2 sets of identical twins, 1 male and 1 female. Of the remaining children there were 71 families with 2 or more sibs at school. 62 of these had 2 sibs at school, 5 had 3 sibs, 3 had 4 sibs and 1 had 6 sibs. In all these families there were only 5 in whom no bruit was heard. 4 of these had 2 sibs and 1 had 3 sibs at school. 8 pairs of the 62 2-sib families had spontaneous bruits—and in no other family did this type of bruit occur in all members. The variable factor of age and the smallness of the numbers make calculations as to the likelihood of familial bruits impossible. However, in this connexion it is of interest to note the following family which we have examined.

(*M.V.H. G.D.* 30280. *P.D.* 30325)

The mother aged 25, (G. D.) attended hospital with a ten-year history of intermittent diplopia and ptosis. The history was strongly suggestive of myasthenia gravis. Physical signs of ptosis and fatiguability and diplopia were thought to confirm this. She volunteered that her son aged 8 (P. D. 30325) had the same condition. He was seen also and the same diagnosis made. They were both admitted to the ward where in each case well defined systolic bruits were heard. The mother's (G. D.) was clearly audible over the right eye and was abolished by occlusion of the right carotid and increased by compression of the left carotid artery. The boy's (P. D.) was clearly audible over the left eye but could also be heard over the right eye faintly. Carotid occlusion in his case brought out the bruit.

Carotid and vertebral angiograms in both cases failed to demonstrate any

anatomical anomalies. The youngest sib aged 4 visited the two in hospital and was noted to have similar facies to the mother and auscultation revealed a clear, right sided, spontaneous bruit over the eye. A third and elder sib aged 14 was asked to attend and was also found to have slight right ptosis and a bruit. Other members of the family were seen, namely the grandmother (aged 68) who had "very heavy lids," the right more than the left, and a clear cut bruit over the left eye. The original patient's (G. D.) sister aged 33 was examined and no bruit found. There were 2 other sibs in this generation who were not available for examination. A further point of interest is that the grandmother, patient G. D. and her sister and two of the 3rd generation had migraine. There was, in addition, a history of asthma in the grandmother and patient G. D. and one 3rd generation child.

The family tree shows these familial features in this case clearly (*see* fig. 1).

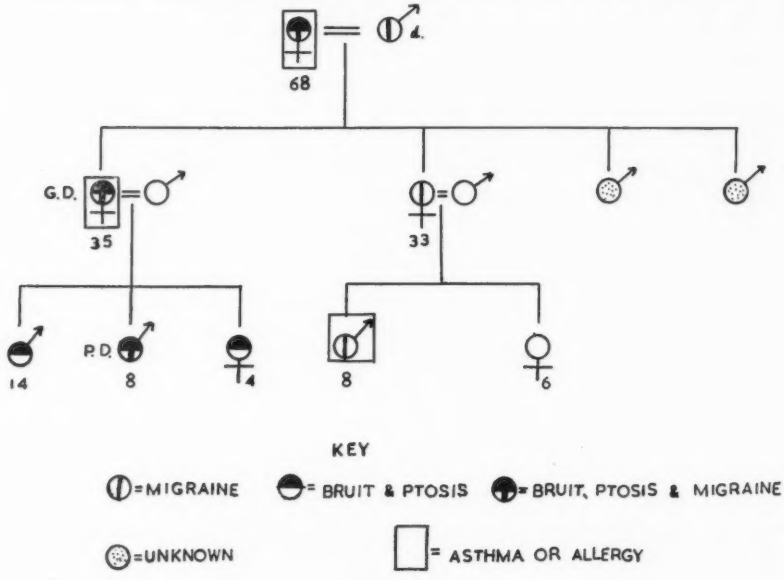


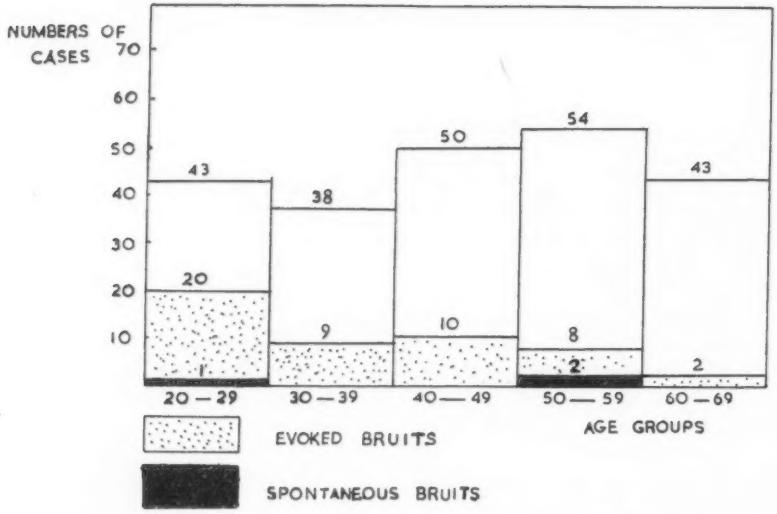
FIG. 1.

B. *Adults.*—In this series we examined 228 patients from the age of 20–69. These patients were seen in the Out-patient Departments and wards of the London and the Maida Vale Hospitals and were not suffering from serious intracranial disease, chest disease (lung or heart) or anæmia. The same technique was employed for these patients as for the children. There were 104 female and 124 male patients. The graph and Table IV shows the case-age distribution and the relative frequency of spontaneous and evoked bruits. It is of great interest that there is over the age of 40 a slow decline in the incidence of evoked bruits, suggesting, perhaps, that this sign is dependent on a resilient vascular bed.

Reference to the table shows that only 3 spontaneous bruits were heard

TABLE IV.

AGE GROUPS	TOTAL CASES	TOTAL BRUITS	EVOKED BRUITS	SPONTANEOUS BRUITS
20-29	43	21	20	1
30-39	38	9	9	0
40-49	50	10	10	0
50-59	54	10	8	2
60-69	43	2	2	0
ALL ADULTS	228	52	49	3



in this group of patients. Of these 3 bruits, one could be ascribed to arteriosclerosis and one was associated with unilateral migraine. Angiograms in this latter case revealed no abnormality—and no explanation for the bruit could be found. The evoked bruits were interesting also in that by far the majority were bilateral, there being only 9 unilateral examples of a total of 57 evoked bruits. Seven of the 9 unilateral cases were female. Apart from this there was no evidence that sex influenced the frequency of these bruits.

Combining the results of this investigation with the frequency of bruits

in health in the children and adults shows an overall persistence of evoked bruits into old age whereas the spontaneous bruits become more and more infrequent and probably do not occur physiologically after middle life. There can be no doubt that in young children and adolescents the presence of a bruit may be a physiological finding in a considerable proportion of cases but there remains a lesser percentage of these patients in whom a bruit may denote vascular anomaly.

Mechanism of Bruits

While it is impossible to be absolutely certain as to the mechanism of these bruits occurring physiologically—there are certain factors that do point to the probable cause. These factors include anatomical and physiological considerations. However, before discussing these factors, it is worthwhile considering the nature of bruits in general. A bruit occurs whenever vibrations are set up within the frequency range of hearing. These vibrations may be created in many ways but by far the commonest mode is by turbulence of gas or fluid. In the special case of vascular or cardiac bruits the noises occur as a result of turbulence in a stream of blood. Turbulence in fluids is the subject of much special study—but it is most commonly produced by (*a*) speeding up the rate of flow in a stream or (*b*) partly obstructing a stream or (*c*) injecting a faster into a slower stream. These mechanisms are common to all freely moving fluids. If, in addition, the fluid contains solid particles, turbulence becomes increasingly easier to produce. From this it will be seen that blood is especially liable to turbulence and the degree of this will determine the presence or absence of a bruit under given circumstances. The problem of the cause of intracranial bruits resolves itself into a search for factors causing excessive turbulence in a part of the cerebrovascular tree in the ways outlined above.

The anatomy of the basal cerebral vessels is very variable. Dandy (1945) reviewed the anatomical variations of the circle of Willis in the light of previous publications in the normal and also in association with congenital aneurysms. The features of greatest interest are first, that in infants and young children there is only slight disproportion between the main cerebral vessels and the communicating vessels (anterior and posterior). With increasing age this disproportion appears to become more marked. Thus over middle age the incidence of thin or even absent posterior communicating vessels rises to 23 per cent (Fetterman and Moran, 1941). It is clear that for the development of an evoked bruit adequate, or perhaps exceptional, channels of communication between the two circulations must exist. De Vriese (quoted by Dandy) in a study of the Circle of Willis showed that in fœtal or infantile Circles only 10 per cent of cases had "small" communicating vessels, whereas, "large" vessels were present in 75 per cent. In considering the mechanism of the evoked bruit it is worth recalling that these are always heard loudest and

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usually only over the eye on the opposite side to the compressed carotid artery. This would suggest that the bruit is made in the anterior cerebral anterior communicating artery segment of the anastomosis, by a greatly increased blood flow. This view is supported by the fact that the majority of our cases with these bruits had them on either side with contralateral carotid compression.

Spontaneous bruits could arise as a result of a congenital asymmetry in the Circle of Willis. Such an asymmetry might favour the shunting of blood from a posterior cerebral artery via the posterior communicating or across the midline via the anterior communicating or equivalent vessel. This mechanism must, however, be very rare and cannot conceivably account for the great frequency of the spontaneous bruit.

A more reasonable solution might be found, in our view, by considering the cerebral blood flow. McMichael and Sharpey-Schafer (1944) studied the cardiac output in adults by cardiac catheterization. They showed that the average resting output was in the region of "4–6 litres per minute while a few have higher outputs up to 10 or 11 litres a minute." They noted that these patients with higher outputs "were in the younger age groups (under 40)," and that they tended to have higher pulse rates. Besterman (1954) studied cardiac output in children with active rheumatic heart disease and compared this with the output in children convalescent from acute rheumatism. The latter group had either no heart lesion or only trivial lesions and had no evidence of active disease. He showed that the output in this control group of 6 children and 1 adult was on an average much higher than the adult figures. The children aged 11–15 years had outputs (with 1 exception) over 12 litres per minute. Unspecified amounts of exertion, raising the pulse rate 28 per minute, increased these output figures to between 15 and 27 litres per minute. There seems some evidence from this work, that the cardiac output is at least equal to, if not more than the adult figure, in children. This high output must be reflected also in the cerebral blood flow. We believe that it is virtually certain that there is a considerably greater cerebral blood flow in children than in adults. It is this blood flow through normal basal vessels in children that creates spontaneous bruits.

In the next section of this paper evidence will be forthcoming from pathological conditions, which we feel strongly supports the thesis outlined above.

Intracranial Bruits in Disease

It is worth recalling here what Cushing (1928) said. "By a strange human frailty, auscultation of the skull seems to be the one thing most likely to be neglected in a routine neurological examination. Cephalic auscultation is a forgotten practice and even when a patient calls attention to the fact that he hears noises in his head, they are so likely to be ascribed to some

form of auditory hallucination or to tinnitus that the examiner rarely thinks of checking the patient's statements with a stethoscope". What was true then is probably more true now, as with the advent of modern methods of investigation, there is a tendency for clinical examination to become of second importance.

Our observations in individuals of various age groups, as stated above, show that the presence of an intracranial bruit below the age of 10 is of doubtful significance unless supported by other clinical evidence. Above the age of 20 the presence of a bruit is of the greatest value in diagnosis in most cases as it arises usually as a result of disturbance of the cranial vasculature.

Of the various conditions in our experience, intracranial angiomas form by far the commonest intracranial cause of cephalic bruit. In a series of 22 patients personally examined by one of us (N. H. W.) a cephalic bruit was heard in 18 (81·8 per cent); of the 4 remaining patients one had a very small entirely venous angioma in which one would not expect to hear a bruit. Different figures have been reported by other authors; and we suspect that the variation depends on whether the series consists of collected cases from hospital records with examinations by different observers over a period of several years, or purely personal observations. The latter often give higher figures. Cushing heard it in 8 out of his 9 cases of arterial angiomas (Cushing, 1928); Mackenzie—50 per cent (Mackenzie, 1953); Paterson and McKissock (1956) noted it in 38 per cent of collected cases from case records; 4 out of 22 in Tonnis' series (1936); Olivecrona and Riives (1948) were of the opinion that it was an infrequent sign of little importance and occurred in only 8 out of their 43 patients.

We believe that care in practising auscultation in all patients especially with epilepsy, migraine or subarachnoid hæmorrhage would certainly disclose more angiomas, although it is claimed that in patients presenting with a subarachnoid hæmorrhage the incidence of bruits is much less than those presenting with epilepsy or migraine (Mackenzie, 1953). The absence of bruit is not certain unless careful auscultation is done over the carotid arteries and specially the globes, preferably in a quiet ward or consulting room.

Apart from cerebral angioma a bruit was heard in the following groups of cases:

(1) Orbital angioma, cirsoid aneurysm, carotico-cavernous fistula, and Paget's disease of the skull.

(2) Tumours—meningioma, glomus jugulare tumour.

(3) Vascular disease—internal carotid artery thrombosis, atheroma of the internal carotid artery, specially in the siphon without actual thrombosis.

(4) General disease—anæmia—thyrotoxicosis. *Mechanism of bruits:*

No single satisfactory and infallible explanation to account for the cause of bruits in cases of different pathology has yet been offered but several theories have been put forward. Selected examples of the conditions noted above will be given which we think throw light both on the particular problem of bruits in disease, and perhaps also in health.

(1) In arteriovenous malformations, carotico-cavernous fistula, Paget's disease of the skull, and in some very vascular tumours of the brain, the mechanism is clearly the one which operates in any arteriovenous shunt; the arterial blood being pumped at pressure into the easily distensible thin-walled veins without a capillary network intervening to grade the pressure down. This is best seen in angioma and carotico-cavernous fistula where the veins may be three times the normal diameter; in the latter condition where the arteriovenous communication is most direct of all and the bruit is the loudest and invariably heard the patients are frequently aware of the bruit. Further, the velocity and volume of blood flowing through the brain in these cases has been shown to be considerably increased and must play some part in the production of the bruit: for instance the cerebral blood flow has been measured in 2 cases of cerebral angioma and found to be three and a half times the normal. (Shenkin, Spitz, Grant and Kety, 1948.) Lassen and Munck (1956)—confirmed these findings amply in 2 further cases and showed that the cerebral blood flow was much faster on the side of the angioma, about four times in one and twice in the other. It is common experience in arteriography of angioma to find the two-second pictures of the series to show a late venous phase normally seen at 6 seconds.

Mackenzie (1955) has suggested another explanation. He argues that in most of the above conditions with increased blood flow the calibre of the appropriate major artery, carotid or vertebral, is increased and there is a relative stenosis, in some cases at the point where the artery enters the intracranial cavity. "It is possible therefore that when a bruit is heard in association with an angioma or other vascular tumour, it originates just beyond the point where the appropriate artery carrying an increased blood supply, undergoes a relative stenosis. This would perhaps explain why some bruits are best heard over the eyeball regardless of the precise situation of the angioma provided that they are supplied by an internal carotid artery. This would also explain why a bruit is not a constant feature of even the largest angiomas." This is an interesting extension of the theory propounded by Fisher (1838) to account for bruits in children. However, there is an alternative explanation as to why a bruit is often best or only heard over the eyeballs. The sound made by the blood rushing through an arteriovenous shunt is conducted along the solid floor of the skull through the sphenoidal fissures to the retro-orbital tissues and is therefore heard more easily over the eyeball. An interesting corollary occurs in cardiac murmurs which may be very difficult to hear

over a thoracoplasty. Mackenzie's explanation can be true in only a small proportion of cases; angiomas in other parts of the body produce a similar murmur which is accepted as a result of the presence of the shunt without invoking the presence of a stenosed hypertrophied feeding artery passing through a bony canal.

The following 2 cases illustrate bruits occurring in patients with gross arterio-venous cephalic shunts.

Case 1.—*D. L., aged* 44. *M.V.H.* 35748

Three months before admission she sustained a trifling head injury and three hours later became aware of a loud rushing noise in the head. This persisted. A month later the left orbit became swollen and the left eye inturned. Examination on admission: palpation of the carotid arteries revealed an arterial thrill on the left, and on auscultation a loud murmur, maximal in systole but continued through diastole. The murmur was heard maximally over the left eye radiating to the left temporal region and left mastoid process. Apart from this murmur there was œdema of both orbits, left more than right with proptosis of the left globe. Carotid angiogram showed a free carotid cavernous communication. Carotid compression on the left side evoked some deterioration of vision in the left eye with mental confusion and it was thought at this stage that ligation was not a safe procedure and she was discharged on 18.4.56.

Readmitted 25.5.56 with increasing left proptosis and pain in the eye of sudden onset. Twenty-four hours before her readmission she noted that the bruit ceased. On examination there was considerable left orbital œdema with chemosis. The left pupil was larger than the right and was fixed. There was a partial 3rd nerve paresis. Auscultation over the eye showed that the bruit had disappeared. She was found to be fibrillating with a pulse rate of 140+ per minute. She was running a mild pyrexia and was found to have a leucocytosis. Over the next few days she became very ill with evidence of multiple systemic emboli and a diagnosis of subacute bacterial endocarditis was certain. It was thought that her signs were produced by embolic occlusion of the internal carotid artery on the left with extension of thrombosis to the cavernous sinus. With intensive antibiotic treatment she recovered wholly but the bruit has never returned.

Case 2.—*E. J., aged* 71 (*L.H.* 16488/48). *Female*

Fifteen years history of gradually developing deformity of the eyes, bridge of the nose and face. Initially there was considerable pain in the bones in which the deformities were developing, especially round the eyes and nose. She also had vague but continual headaches. Over the last few years there has been little change and the pain has subsided. Thirteen years ago she started seeing double, this lasted for a few years till she started losing vision in the left eye. She has been unable to see out of the left eye for five years and more recently has noticed failing vision in the right eye. Gradully increasing bilateral deafness for fifteen years.

On examination gross facial deformity mostly confined to the maxillæ and the bones of the orbits. No deformity of the mandible (figs. 2 and 3, Plate LXIII). No other bonyabnormality. A distinct loud low pitched bruit heard over the left temple. Bilateral optic atrophy. V.L.O., V.R. 1/60. Rest of the nervous system normal. X-rays show changes of Paget's disease.

Two further points should be mentioned. Cardiac output has been found to be greatly increased in generalized Paget's disease. We do not feel that this is likely in this particular case since the bony changes were

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localized to the skull. Involvement of the base of the skull could theoretically cause atresia of the carotid arteries. Basal films here do not show involvement of the carotid canal; physical examination it will be noted showed no involvement of the trigeminal nerves. The bruit was considered to be due to a gross arterio-venous shunt in the affected bones.

(2) A loud bruit may be heard in an intracranial tumour without the tumour's being necessarily vascular. Whether it is due to hydrocephalus, or distortion of the arterial tree (Josefson, 1929) or the presence of large feeding vessels entering a tumour, is uncertain. If it is from the former cause then it is surprising that not more patients with hydrocephalus have bruits.

Case 3.—*H. F., aged* 16. (*L.H. No.* 13759/54). *Female.*

Three years left-sided tinnitus; morning nausea and vomiting for two years. For two months sporadic headaches, occasionally feeling dizzy as though she might faint. No loss of consciousness, no deterioration of vision or double vision. School work satisfactory. On examination pronounced loud bruit heard all over the left side of the skull and forehead and very faintly on the right. Carotid arteries equal. No papilloedema. Definite horizontal nystagmus. Tendon reflexes brisk in the arms, exaggerated in the legs, plantar responses flexor. Investigations revealed gross hydrocephalus from a posterior fossa tumour. The bruit was thought to be due to hydrocephalus. At operation a large posterior fossa tumour was found—this was an ependymoma of the fourth ventricle, histologically confirmed. The only point of interest was that during operation the left posterior inferior cerebellar artery was found to be "much fatter than the right and before it reached the tumour it had taken a complete circle as a loop below the tumour over the posterior aspect of the cord, that is to say it was down below the arch of the atlas." Both arteries took a sinuous course slightly adherent to the tumour and then passed into the depths of the cerebellum.

It is possible that the mechanism of this bruit was due not to hydrocephalus but to an increased blood-flow through the large sinuous posterior inferior cerebellar arteries. Dalsgaard-Nielsen (1939) mentions two similar cases.

Case 4.—*E. M., aged* 53 (*L.H. No.* 26607/54) *Female. Admitted* 23.10.56.

Two years history of progressive dementia leading to complete confusion and disorientation at the time of admission. Vague headaches in the left fronto-temporal region for the same period and a pulsating noise in the left ear. Clumsiness of the right hand and disturbance of vision in the last few months.

On examination verbose, disorientated in time and space, agitated; some evidence of expressive weakness of the right face, deep reflexes exaggerated more on the right than left, plantars flexor. Angiography revealed a large left sphenoidal ridge meningioma which was extremely vascular; the left middle cerebral artery was pushed up considerably and stretched: the internal carotid seemed to be stretched and narrowed just before its bifurcation, the rest of the siphon being of normal calibre.

This is a good example of the causation of a bruit in a meningioma. The vascularity of the tumour is one factor, but more important we think

is the stretching and sudden narrowing of the internal carotid artery (figs. 4 and 5, Plate LXIV). This is supported by the fact that after a sub-temporal decompression her bruit disappeared.

She was treated with sub-temporal decompression and deep X-ray therapy, with a view to more radical surgery at a later date.

(3) Bruits in patients suffering from atheroma of the internal carotid artery are due either to blood going from a narrower to a wider and relatively more normal part of the artery or to blood rushing past a large atheromatous plaque protruding into the lumen of the artery. Mackenzie (1953) gives a case of this kind and our next example showed exactly comparable findings on angiography.

Case 5.—J. K., aged 65. *Admitted* 9.7.54. (*L.H. No.* 23963/54).

Eight years before admission sudden weakness of the right leg which improved after a few days.

Eight months prior to admission developed a similar weakness in the left arm and leg. This got slightly worse over the next week, but there was no change then up to the time of admission. No headaches or speech defect.

On examination there was considerable peripheral arteriosclerosis, blood pressure 160/95, a well marked high-pitched bruit was heard over the right eye and carotid artery. Fundi normal. Slight weakness of the left arm, mostly proximal, and moderate weakness of the left ankle, expecially in dorsiflexion and eversion. Increased tone in both lower limbs, left greater than right. Indefinite loss to pin-prick over the foot and lower half of the left leg, touch and temperature appreciation normal. Impaired vibration sensation in the left foot. Reflexes were all exaggerated on the left side and to a lesser extent in the right leg. Left abdominals were absent, the right plantar was equivocal and the left extensor. Skull X-rays EEG and c.s.f. examination revealed no abnormality. A right carotid angiogram showed no evidence of thrombosis but the right internal carotid artery at the level of the siphon was narrowed and irregular. There can be no doubt that the diagnosis here was cerebrovascular disease with atheromatous narrowing of the right internal carotid artery and that the latter was the cause of the bruit.

The same mechanism acts in a partly thrombosed artery. However, the presence of a bruit over the eyeballs in a completely occluded artery is of great interest and significance. It seems to us that by occluding one carotid artery, blood goes through the anterior communicating artery and in so doing produces a noise which we hear as a bruit. Why it is heard in only a few cases and not in all of them is a matter for conjecture, but it must depend on the calibre and condition of the anterior communicating artery, the rate of blood flow, and the presence of alternative channels of blood flow such as the contribution of the external carotid artery through the ophthalmic artery on the side of the blocked internal carotid. If this latter contribution is large the anterior communicating artery may not have enough blood shunting through it to produce a bruit. A brief account of this mechanism of bruit production in cases of internal carotid artery thrombosis can be best shown by the following case report.

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Case 6.—*H. F., male, aged* 61. (*L.H. No.* 40259/55).
First admission 11.5.56.

In May 1955 temporary paralysis of the right arm lasting for five minutes, followed by numbness of the right leg. November 1955, an episode of total blindness in the left eye for two to three minutes. This transitory blindness occurred a dozen times in the next fortnight, still leaving the eye perfectly normal. One further attack of paralysis of the right side in late November 1955. On examination the carotid arteries were equal, a bruit was heard over both eyes but much louder on the right than on the left. Fundi and cranial nerves were normal and there was no impairment of visual acuity. All reflexes were exaggerated, right more than left, with right plantar extensor and the left equivocal. A diagnosis of left internal carotid artery thrombosis was confirmed on angiography and later at operation on exploration of the neck with a view to arterial graft, or disobliteration; the latter procedures were not carried out as the thrombosis was extending high up the artery.

Second admission 25.8.56.—Patient remained well until a few days before admission, when he developed weakness of both legs and of the left arm. The night before admission he complained of pains in his legs, his speech became slurred and he was mentally confused. On the day of admission he developed a complete left hemiplegia. On examination at this time the right carotid pulse was less than the left, the bruit previously present had completely disappeared, he was drowsy and confused but there was no dysphasia, he was dysarthric with great increase of tone in all four limbs and total paralysis of the left side, the right side was moderately paralysed, all reflexes were exaggerated and the plantars were extensor. A diagnosis of recent right internal carotid artery thrombosis was made but it was thought unnecessary to confirm it by angiography in view of his general arteriosclerotic state. He made considerable improvement and at the time of his discharge six weeks after admission he was mentally clear; there was still a left hemiparesis with only slight weakness of the right side.

We think the mechanism of the bruit on the first admission was due to blood being shunted from the right to the left hemisphere from a patent right internal carotid artery through the anterior communicating artery. When the right internal carotid artery became occluded at a later date the bruit disappeared.

Some excellent work has been done on the cerebral circulation by McDonald and Potter (1951). Symonds (1955), in his Harvian oration sums it up concisely. "Thus there are virtually three separate streams of arterial blood supplying the brain, one from the basilar and one from each internal carotid artery, separated from one another not by any physical barrier but by the dead points in the posterior and anterior communicating arteries, the position of each of these dead points depending upon the balance of pressure in the opposing streams. When one artery is occluded—the corresponding arterial pressure falls. There must be a shift of the dead point in the anterior communicating artery and a flow of blood from the unobstructed side to fill the anterior and probably the middle cerebral arteries on the obstructed side . . . The anterior communicating artery to do this must be of an adequate diameter."

The importance of the anterior communicating artery in shunting blood

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from one side to the other has been shown by us earlier on in the paper: by compression of one carotid artery a bruit can be produced in a large number of patients under the age of 20. The significance of the presence of such a bruit may be of importance in trying to assess the cerebral circulation before tying the internal carotid artery in treatment of patients with intracranial aneurysms.

(4) We have listened over the globes and carotid arteries in many cases of anæmia and thyrotoxicosis, and it is our experience, especially in the former, that bruits are a very common finding in moderately severe cases. Anæmia has been mentioned as a cause of intracranial bruits by many authors over the last 90 years. (Henoch, 1861; Osler, 1880; Still, 1921; Sears, 1938.) Sears (1938) thought that the bruit heard in thyrotoxicosis was conducted from a hypervascular thyroid gland.

In our experience in anæmia it is not the variety but the severity that matters. A bruit is almost invariably present with a hæmoglobin level of 50 per cent or less. The origin of these bruits is entirely intracranial and they are not merely conducted from more distant parts. We have heard bruits over the globes suppressed by occlusion of the appropriate carotid artery in patients who had no precordial murmur associated with their anæmia. The explanation must be similar to that of the hæmic cardiac murmur. Schmidt (1950) points out that the cerebral blood flow is very high and the cerebral vessel resistance very low in anæmia. This allows blood to travel at great speed through the cerebral vessels evoking a bruit.

A similar state exists in the cerebral circulation in thyrotoxicosis according to Sokoloff *et al.* (1953) and we have heard bruits over the globes which have not been conducted from the thyroid gland.

Conclusions and Summary

In contrast to other authors we find cephalic bruits to be extremely common in young children—but that their incidence falls off appreciably at the age of 10 years. Throughout adult life spontaneous bruits are rare as a normal finding—we have 3 possible examples in a material of 228 cases. Evoked bruits, however, persist as a fairly frequent finding well into middle life, after which there is a marked fall with increasing age.

We feel that these findings are to be correlated with the anatomy of the Circle of Willis combined with the variable factor of cerebral blood flow. There is some evidence to suggest that bruits may be familial on some occasions. This may well be saying in another way that anatomical variations of the Circle of Willis may be familial.

We believe that spontaneous bruits in children are caused by a relatively high cerebral blood flow through comparatively narrow main basal arteries. As the cerebral blood flow falls with adolescence and the main basal vessels

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become comparatively wider they contain a less turbulent stream and the bruits become less frequent.

Evoked bruits are produced by blood flowing freely through the communicating arteries, both anterior and posterior. This would seem to be supported by the fact that these bruits are infrequent after middle life—a time when vascular resilience is fading. Clearly, two conditions are essential to bruit production. There must be an adequate channel and an adequate blood flow or volume. If the channel is too narrow insufficient blood volume or flow passes through to create the turbulence that is translated to a bruit.

Review of the cases we have cited above reveals factors common to them all. First, the cerebral blood flow of one hemisphere has altered so as to be increased or decreased. The effects of this are that extra blood has obviously to come to the affected hemisphere from the opposite side. In the case of angioma and vascular tumours, the increased blood flow comes through hypertrophy of existing vessels on the same side as well as "robbing" the opposite hemisphere. Second, a direct consequence of the above, at some point or points the local blood flow in terms of velocity and volume is greatly increased. Third, in those extracranial causes of bruits, the cerebral blood flow per minute is markedly increased matching the increased cardiac output.

The first two factors almost certainly produce the necessary blood flow through the communicating vessels to evoke bruits in the same way that they may be evoked in children. Finally, in those cases of anæmia and thyrotoxicosis where an increased cerebral blood flow occurs, arising from an increased cardiac output, a bruit will be caused by the turbulence in the basal vessels. This bruit is precisely analogous to that occurring spontaneously in children.

We wish to acknowledge the help given by Dr. R. Evans, Medical Officer of Health, and the Carmarthenshire County Council Education Committee.

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REFERENCES

BEADLES, C. F. (1907) *Brain*, **30**, 285.

BESTERMAN, E. M. M. (1954) *Brit. Heart J.*, **16**, 8.

CUSHING, H., and BAILEY, P. (1928) "Tumors Arising from the Blood Vessels of the Brain." London. Baillière, Tindall and Cox.

DALSGAARD-NIELSEN, T. (1939) *Acta psychiat., Kbh.*, **14**, 69.

DANDY, W. E. (1945) "Intracranial Arterial Aneurysms," New York.

DE VRIESE, B. (1905) *Arch. Biol., Paris*, **21**, 357.

PLATE LXIII

FIG. 2.

FIG. 3.

To illustrate article by N. H. Wadia and G. Monckton.

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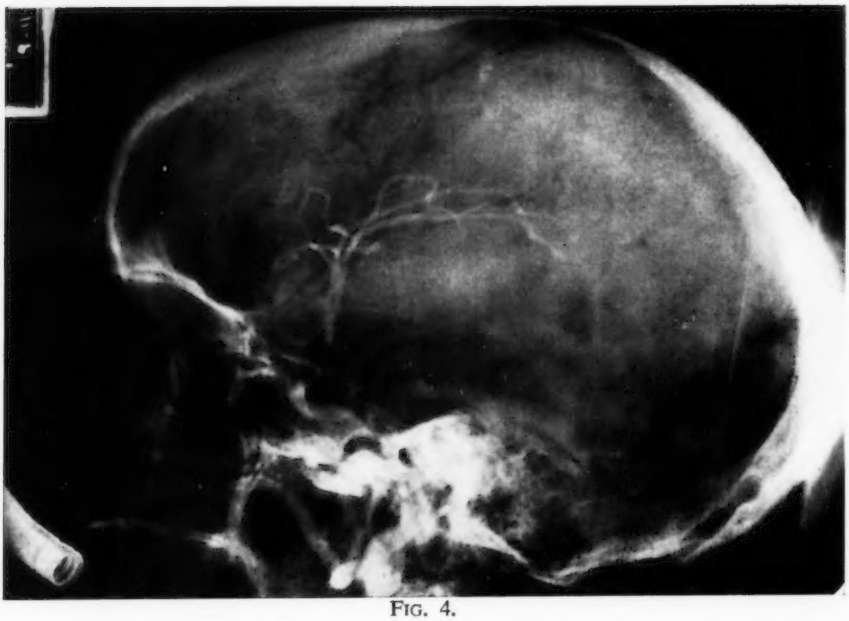

FIG. 4.

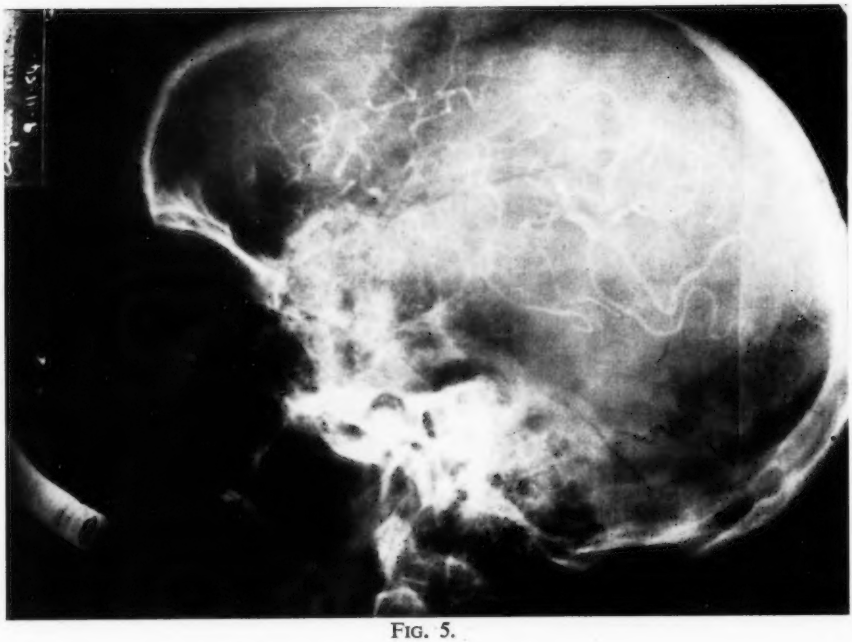

FIG. 5.

To illustrate article by N. H. Wadia and G. Monckton.

DODGE, H. W., Jr. (1956) *J. Neurosurg.*, **13,** 527.
FETTERMAN, G. H., and MORAN, T. J. (1941) *Arch. Path.*, **32,** 251.
FISHER, J. D. (1834) *Med. Mag., Boston.*, **2,** 144.
—— (1838) *Amer. J. med. Sci.*, **22,** 259, "Observations on Cerebral Auscultation."
HAMBURGER, L. P. (1931) *Amer. J. med. Sci.*, **181,** 756.
HENNIG, (1856) *Arch. physiol. Heilk.*, **15,** 411.
HENOCH, E. (1861) "Beitrage zur Kinderheilkunde." Berlin.
JOSEFSON, A. (1929) *Hygiea, Stockh.*, **91,** 545.
LASSEN, N. A., and MUNCK, O. (1956) *Acta psychiat. et Neurol. scand.*, **31,** 71.
MCDONALD, D. A., and POTTER, J. M. (1951) *J. Physiol.*, **114,** 356.
MACKENZIE, I. (1953) *Brain*, **76,** 184.
—— (1955) *Brain*, **78,** 350.
MCMICHAEL, J., and SHARPEY-SCHAFER, E. P. (1944) *Brit. Heart J.*, **6,** 33.
OLIVECRONA, H., and RIIVES, J. (1948) *Arch. Neurol. Psychiat., Chicago*, **59,** 567.
OSLER, W. (1880) *Boston med. surg. J.*, **103,** 29.
PATERSON, J. HAMILTON, and MCKISSOCK, W. (1956) *Brain*, **79,** 233.
ROGER, H. (1883) "Recherches Cliniques pour les Maladies de L'enfance." Paris, Vol. **2,** p. 261.
SCHMIDT, C. F. (1950) "The Cerebral Circulation in Health and Disease." Springfield, Ill.
SEARS, W. G. (1938) *Guy's Hosp. Rep.*, **88,** 308.
SHENKIN, H. A., SPITZ, E. B., GRANT, F. C., and KETY, S. S. (1948) *J. Neurosurg.*, **5,** 165.
SOKOLOFF, L., WECHSLER, R. L., MANGOLD, R., BALLS, K., and KETY, S. S. (1953) *J. clin. Invest.*, **32,** 202.
STILL, C. F. (1921) *Brit. J. Child. Dis.*, **18,** 173.
SYMONDS, C. P. (1955) *Brit. med. J.*, **1,** 119.
TONNIS, W. (1936) *In* Bergstrand, H., Olivecrona, H., and Tonnis, W. "Gefassmissbildungen und Gefassgeschwulste des Gehirns,' Leipzig. (Georg Thieme).
WIRTHGEN, G. (1855) Inaug. Diss., Lipsiæ.
WHITNEY, S. S. (1843) *Amer. J. med. Sci.*, **6,** 281.

LEGENDS FOR PLATES

PLATE LXIII

FIGS. 2 and 3.—Paget's disease of skull.

PLATE LXIV

FIGS. 4 and 5.—Showing arterial and capillary phases of carotid angiogram. Note stretching and narrowing of the internal carotid artery, and the vascular blush of the meningioma.

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THE BRAIN-STEM CONCEIVED AS THE "HIGHEST LEVEL" OF FUNCTION IN THE NERVOUS SYSTEM; WITH PARTICULAR REFERENCE TO THE "AUTOMATIC APPARATUS" OF CARPENTER (1850) AND TO THE "CENTRENCEPHALIC INTEGRATING SYSTEM" OF PENFIELD

BY

F. M. R. WALSHE

I. Introduction

The concept of "levels" in the physiological hierarchy within the nervous system we owe to Hughlings Jackson, and it is not proposed now to discuss the particular roles he attributed to the levels he postulated. It suffices to say that the concept was a physiological and not a morphological one, though necessarily each level of function had its morphological substratum which he designated as its "anatomy," using this term to refer to a group of structures as engaged in a co-ordinated activity: that is, referring to structures in their functional relationships.

Further, as we know, the concept of levels was based, not primarily upon a speculative or a philosophical basis, but as an inference from facts of clinical observation, comprising the motor disorders of chorea, of convulsions beginning unilaterally, and the patterns of motor disorder ensuing upon destroying lesions of the brain.

This review deals with a new concept of levels elaborated by Penfield and compares it with a similar concept that was widely held a century ago when it was formulated by W. B. Carpenter, the author of the standard textbook of physiology at that time.[1]

Jackson's was perhaps the first modern generalization about the nervous system as a co-ordinating system that was based on observation rather than on affirmation. Moreover, it was unique in that it rigorously excluded psychical activities from the dynamic properties of the nervous system, which for Jackson was solely a system for the co-ordination of impressions and movements. Adopting the doctrine of psychophysical

[1]W. B. Carpenter (1813–1885) was Professor of Physiology and of Forensic Medicine at University College and Hospital, London. He wrote two textbooks on physiology and was a prolific writer of papers on zoology, botany and physiology. The references given in this article are from his "Principles of Human Physiology," 4th English edition, 1853. There were also a number of American editions of this work.

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parallelism, he wrote of the nervous system, as did Sherrington, in the language of anatomy and physiology, and expressed himself as not competent to solve the metaphysical problem involved in the nature of the relationship of brain to mind.

II. Carpenter's "Automatic Apparatus"

These preliminary remarks serve to precede and to introduce a brief account of the state of physiological opinion concerning some dynamic properties of the nervous system, as it was a century ago, prior to the formulation of Jackson's concept of levels.

At the mid-period of the nineteenth century the human brain was generally credited with both psychological and physiological activities. By psychological properties are meant conscious mind, and also certain cortical activities described by Carpenter as "unconscious cerebration" and enumerated by him as emotion, reason, ideas, and Will.

During the earlier years of the century the current view was that expressed by Johannes Müller, namely that the sole seat of consciousness was the medulla oblongata, but from about 1850 to the early 1870s physiological opinion in England and the United States was expressed in, and we may suppose was largely formed by, the successive editions of Carpenter's "Principles of Human Physiology."

It is with Carpenter's hypothesis of a dominating role of the thalamus and the sensory ganglia, which together he named the "automatic apparatus," that we are now concerned. Its interest is not merely historical, but topical also in that it appears to be the prototype of Penfield's concept of a "centrencephalic integrating system," evolved a century later but closely resembling Carpenter's concept almost, indeed, as though the intervening century had not profoundly added to our knowledge of the brain and revolutionized many of our ideas of its activities.

Carpenter approaches the question from the point of view of the neural seat of consciousness, and to clarify and to state summarily his attitude towards the question of the brain-mind relationship, I may quote him (p. 795) as follows: "Of the nature of the connexion between nervous action and mental action, we can form no distinct idea. Few physiologists would be disposed to deny that the cerebrum is the instrument of psychical powers: and yet no one has been able to form a self-consistent theory of the mode in which this is so."

The operative sentence here is somewhat equivocal, but we find Carpenter everywhere speaking of various psychical manifestations and activities as being functions of the brain. This allows him to pass freely in his discourse between psychological and physiological categories. The arrangement is an extremely convenient one for any expositor of brain function who does not desire to face the issue involved when it arises.

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For Carpenter the sensory ganglia are the sole seat of consciousness, and he enumerates these ganglia as the olfactory bulbs, the corpora quadrigemina, the auditory and gustatory ganglia in the medulla, with, as their common focus, the optic thalamus: the last-named being the central termination of the sensory tract. There is, he says (p. 726) "a complete *physiological* separation between the cerebrum and the sensory ganglia upon which it is superimposed." These ganglia are not mere appendages to the cerebrum but independent centres. It is in these centres alone that sensations enter consciousness, and in addition they form together "the immediate centres of the motor influence" which excites muscular movements. The motor tracts arise in the corpora striata.

The thalamus and the sensory ganglia together constitute the "automatic apparatus," which is the essential substratum of the integration of sensation and movement. Thus constituted, the apparatus may be set in action either from above, that is, from the "vesicular matter" of the cerebral cortex (the convolutions), or from below by way of the sensory tract from the periphery. The first source of activation is most important in man since it embodies "the guidance of reason" (p. 740), and, thus activated, the sensory ganglia are the instruments by which our voluntary movements are formed, directed and controlled (fig. 1).

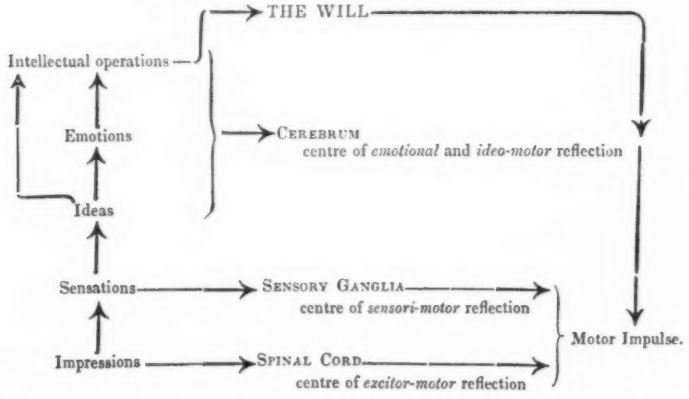

FIG. 1.—Carpenter's diagram indicating his general concept of the plan of the automatic apparatus and its relation to the cerebral cortex. They should be compared with Penfield's two diagrams (figs. 6 and 7) in *Brain*, **77**, 1.

Paradoxically, although the cerebral convolutions provide the guidance of reason, their activities are not attended by consciousness, and Carpenter presents a long argument to the effect that there is no inherent need to postulate consciousness as attendant upon cortical activity, indeed this

activity is specifically referred to as "unconscious cerebration" (p. 819). What happens, he explains, is that sensory impulses from the periphery enter consciousness in the sensory ganglia. Here fresh impulses arise and are transmitted to the cerebral cortex in which they evoke changes that evolve "nerve force." The products of this force are variously named as ideas, emotions, reasoning processes, emotional or volitional determinations or as the Will. These, operating unconsciously, react back upon the sensory ganglia; that is, upon the automatic apparatus, which in its turn reacts upon the motor tract and nerves and the muscles.

Further, the emotional and volitional determinations, etc., become consciously entertained in the sensory ganglia which "constitute the seat of consciousness, not merely for impressions on the organs of sense, but also for changes in the cortical substance of the cerebrum: so that, until the latter have reacted downwards upon the sensorium (i.e. sensory ganglia), we have no consciousness either of the formation of ideas, or of any intellectual process of which they may be the subject" (p. 779).

The manner in which the Will or the emotions produce muscular motion through the automatic apparatus is further discussed by Carpente thus: "now it may be asserted with some confidence that no effort of the Will *can* exert direct influence upon the muscles . . . the Will is solely concerned in determining the result, the selection and combination of muscular movements required to bring about the result *not* being effected by the Will, but by some intermediate agency. If it were otherwise, we should be dependent upon anatomical knowledge for our power of

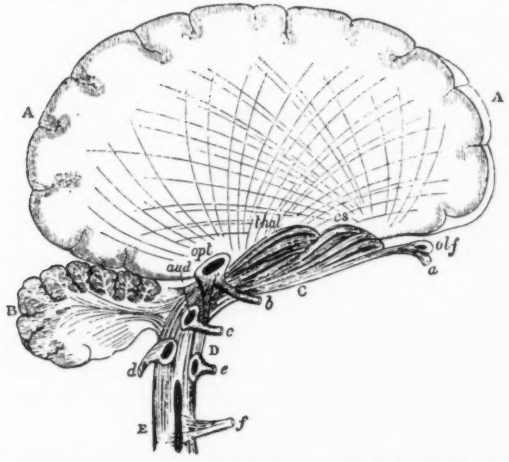

FIG. 2.—Carpenter's fig. 137. It reveals the cerebral hemisphere connected with the sensory ganglia, the brain-stem and the cord by radiating fibres (Reil's "nerves of internal sense").

cs (corpus striatum), thal (thalamus), C (sensorimotor tract.)

performing the simplest movements of the body whereas we find the fact to be that man who has not the least idea of the mechanism of muscular action can acquire the most perfect command of his movements" (p. 747). Again, "it is obvious that we have to seek some intermediate agency which executes the actions determined by the Will . . . even voluntary movements are executed by the instrumentality of the automatic apparatus" (p. 749) (*see* fig. 2).

Hence, the cerebral cortex is conceived as having no role in the co-ordination of movements, being dependent for this upon the automatic apparatus. The sensory ganglia also provide the "guiding sensations" that underlie this co-ordination. Thus, the seat of the integrative action of the nervous system is the automatic apparatus.

Some further reference is necessary to the role of this apparatus and that of the cerebral cortex in consciousness. On this, Carpenter says as follows: "It is an enquiry of considerable interest, both in its psychological and physiological relations, whether the cerebrum itself is endowed with consciousness: that is, whether we become conscious of changes which take place in its substance so long as these changes are limited to itself. At first sight it would appear to be a very startling proposition, that the organ of intellectual operations is not itself endowed with consciousness: but a careful consideration of its relations to the sensory ganglia will tend to show that there is no *a priori* absurdity in such a notion . . . it can scarcely be deemed unlikely that the sensorial centres should be the seat of consciousness, not merely of impressions transmitted to them by the nerves of the external senses, but also of the impressions brought to them by the "nerves of the internal senses," as the sagacious Reil designated the radiating fibres of the cerebral hemisphere. . . . And there is on the other hand an *a priori* improbability that there should be two seats of consciousness, so far removed from one another as the sensory ganglia and the vesicular surface of the hemispheres" (p. 778). "We are led," he continues, "by the very cogent evidence which comparative anatomy supplies, to regard this series of ganglionic centres as constituting the real *sensorium;* each ganglion having the power of communicating to the mind the impressions derived from the organ with which it is connected, and of exciting automatic muscular movements in respondence to these sensations. If this position be denied, we must either refuse the attribute of consciousness to such animals as possess no other encephalic centres than these; or we must believe that the *addition* of the cerebral hemispheres, in the vertebrated series, *alters* the endowments of the sensory ganglia—an idea which is contrary to analogy" (p. 729).

Through the "unconscious" activity of the cortex there come to life, as it were, in the sensory ganglia, "ideational consciousness, emotional consciousness, intuitional consciousness and logical consciousness," "In the end," he says, "it will be found much simpler to accept the doctrine of

a common centre for sensation and for what may be distinguished as mental consciousness, than to regard the two centres as distinct" (p. 779). Finally, Carpenter also makes the sensory ganglia the seat of memory, for since a memory is only a sensation recalled by a "cerebral act," where should it be found if not in the sensory ganglia, that is, in the place where it first dawned upon consciousness?

We have already noted Carpenter's dislike of the idea of a spatial separation between the seat of "sensation" and that of "mental consciousness." The former, known as the *sensorium commune*, had been regarded as "a collective unity of perceptions" before Carpenter's time, and he thinks it simpler that the two modes of consciousness should share a common seat, and he urges also that it is contrary to analogy to suppose that the function of the brain-stem centres that subserved the entire consciousness of some lower animal forms, should migrate to the cerebrum, when in the course of evolution this organ developed.

Yet no such misgivings seem to beset him when he separates the "unconscious cerebration" of the cerebral cortex from "memory," which he places in the sensory ganglia; and how it happens that the canon of simplicity in nature which he has invoked does not apply here he does not explain, though it is surely strange that intellectual operations, albeit unconscious, should be separated from memory by these topographical dispositions which he postulates.

And with the word "postulates," we approach the question of the factual basis, the observational foundations, of all this hypothesizing. Is there, in his account, anything at all that he or any other physiologist had observed at that date, to justify these attributions of functions psychical and physiological to the structures named?

Of the sensory functions of the olfactory bulbs and corpora quadrigemina and the auditory and gustatory nuclei something was indeed known, but that with the thalamus they constituted an automatic apparatus controlling motion and integrating sensation, and, in addition, that they were in the human subject the seat of all modes of consciousness, there was no evidence.

In short, Carpenter's automatic apparatus, as he conceived it, was the child of ratiocination and not of observation. It was an intellectual exercise carried out in the dark void of contemporary ignorance of cerebral functions, and not adequately illuminated by what was then known of the reflex functions of the spinal cord. There is an air of the synthetic about it.

This doctrine remained in Carpenter's textbook up to the last edition for which he was responsible, and he was not alone in his views, for his contemporary, Thomas Laycock, one of Hughlings Jackson's early teachers, sums up the matter in the same sense as does Carpenter, but

more succinctly, in his two-volume work entitled, "Mind and Brain: or the correlation of Consciousness and Organization," published in 1860. There he writes that "the medulla oblongata is the common sensory of *all* conscious states, whether they refer to corporeal processes, or to the purely encephalic changes associated with ideas. The cerebral and the cerebellar hemispheres may be considered as extensive peripheries, having, like the corporeal periphery, the medulla oblongata as their centre."

In short, the reader of these expositions must be struck by the relatively minor part borne by observation in them, and the predominance of simple affirmation[1] as the foundation of the entire theoretical structure.

But this was neither the first nor is it the last general theory of function in the nervous system to which the same criticism may be said to apply. In their critique of the concept of the afferent nervous system proposed by Head and Rivers, Trotter and Davies (1913, p. 35) remark, "In dealing with theoretical considerations concerned with the physiology of the nervous system, one is exceptionally liable to be misled by preconceived or introspectively involved notions as to how sensory and perceptive processes may be supposed to act. Symmetry and the desire for classification are apt to be mistaken for physiological principles and we tend to drift into the error of supposing that conceptions which are clear-cut easily comprehensible and "reasonable" acquire by that very fact an increased probability of being accurate expositions of the physiological processes they profess to explain. This has been repeatedly demonstrated in the history of neurology . . . physiological necessity is apt to defy our preconceived notions of reasonableness and to escape any classification which is more respectful of logic than of fact."

It may be asked why, if Carpenter's automatic apparatus with its congeries of high level mental and neural functions was merely an intellectual *tour de force* without substance, we should devote so much time and attention to it today. In 1850 Carpenter was exploring beyond the frontiers of knowledge and trying to penetrate the secrets of central nervous function, and the criticism we may make of him, perhaps, is that he sought to do by speculation what could be done only by research, clinical or experimental.

Today, we also are seeking to extend the frontiers of knowledge by appropriate methods of investigation, inspired sometimes no doubt by shrewd hypothesis as a means. It must be of interest, therefore, for us to look back upon the practical and the intellectual methods of our forebears in neurology, to learn by their mistakes not less than by their achievements. We are better placed to investigate now than a century ago, but what has been gained since 1850 cannot, upon the most sanguine

[1]The word "affirmation" does not belong to the grammar of science, and must therefore be defined. It is used here as referring to a factual proposition for which no observational data, demonstration, or proof are offered.

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estimate, be said to have brought the solution of the many problems of cerebral function within sight. In respect of the magnitude of the problem that still remains, our achievements, though considerable, are relatively small. We are not so very differently placed from Carpenter after all, and it is not without point to consider whether our methods are as different and as improved as we wish to believe. That speculation still runs ahead of fact in electrophysiology is the theme of a stimulating paper by O'Leary (1956), to whom some years ago the present writer owed his introduction to Carpenter's book.

Therefore the latter's concept of an "automatic apparatus" located mainly in the brain-stem, and endowed with a wide range and variety of psychological and physiological control within the organism, may be worth study as a prototype of a later essay in the same order, and one making even wider claims.

III. Penfield's "Centrencephalic Integrating System"

(*a*) *General Considerations*

Like Carpenter before him, Penfield was led to the concept of a centrally placed unifier of neural function, having both mental and physiological activities, by the problem of consciousness and by a felt need to localize this state or function somewhere within the nervous system. He avows this quite clearly in his first paper (1938) upon the subject. "It seems quite proper," he states, "that neurologists should push their investigations into the neurologic mechanism associated with consciousness and should enquire closely into the localization of that mechanism without apology and without taking responsibility for the theory of consciousness." "To make such an enquiry," he continues, "is to ask a very old question," and how old indeed it is, he indicates by a quotation from the Book of Job:

> "Where shall wisdom be found?
> And where is the place of understanding?"

He ends the paper by defining the "place of understanding" as "the location of those neuronal circuits which are most intimately associated with the initiation of voluntary activity and with the sensory summation prerequisite to it."

The readers of the papers in which over the past twenty years Penfield has expounded this doctrine will know that this "location" is the "centrencephalic integrating system," as he later came to call it.

We have here a concept that is far more than an essay in pure physiology, despite Penfield's disclaimer of any responsibility for a "theory of consciousness." It is natural that he should wish to avoid a question that has baffled philosophers and confused physiologists for generations. Yet in postulating a precise anatomical localization, extended in space, for what William James has called the function of knowing, he surely cannot escape some responsibility for the definition of what he proposes to

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localize. Can we locate the undefined, which may well prove indefinable in the grammar of physiology?

As we have seen, Carpenter evades this difficulty by using indifferently the grammars of both psychology and physiology, on a basis of pure expediency, as though they referred to phenomena and ideas of the same order. When a process cannot be formulated in the language of physiology because not enough is known about it, he falls quietly back upon that of psychology, and the passage from "nerve force" to "volitional determinations" is scarcely noticed. This is the method adopted by Penfield also throughout his expositions of the centrencephalic system.

We see it, for example, in the placing in the temporal cortex of "a psychical circuit," and in the reference to "the discriminative nature of the stream of impulses," as though the physico-chemical change that takes place at the surface of the neural conductor had mysterious psychological faculties. The convention is that of Head, who endowed the nerve impulse with "feeling tone" when it traversed the protopathic system, and postulated a pathway for the concept we call localization.

This preliminary adumbration by Penfield of a centrally placed integrating mechanism within the brain and dominating it, with its corollary of a search for a local mechanism of consciousness, represents an attitude in facing the problems of life and mind that not every biologist shares. To those who do not share it, there is a strong sense of anti-climax in the seriously proffered hypothesis that some neuronal circuits in the brain-stem can be the seat of wisdom and the place of understanding.

Perhaps for the neurosurgeon, in his natural preoccupation with space-occupying lesions, it is easy to come to think of consciousness as a space-occupying entity with a room of its own in the brain-stem: choosing this place because he has found that lesions here may be accompanied by coma, and drawing thence the conclusion that coma's supposed opposite, consciousness, must surely reside here. As Penfield (1951) puts it, "the seat of consciousness is that portion of the nervous system in which circumscribed injury or functional inactivation produces loss of consciousness. On the basis of our present information this would place the seat of consciousness somewhere in the higher brain-stem."[1]

Yet in so thinking, he is unwittingly, we must suppose, reverting to an old and abandoned view, for from the late eighteenth century (cf. O'Leary, 1956) the brain-stem was the favoured site for consciousness, until in 1850 Carpenter added the thalamus. But after 1870, the *sensorium commune* disappeared from the literature, and Schäfer (1900) summing up the literature tells us that at the end of the nineteenth century the cerebral

[1]To preserve chronology, it is noted that all references to Penfield (1951) refer to a paper read at the International Neurological Congress in Paris in 1949, but not published until two years later.

cortex was generally accepted as the seat of "the intellectual functions, intelligent sensation or consciousness, ideation, volition and memory." By this time, as O'Leary observes, Carpenter's theory had become "a neglected guess, to be revived only recently."

Penfield's concept of a highest level integrating system in the brain-stem is essentially based, it would seem, upon observations made by him in the course of the surgical exposure of the human cerebral cortex. An extended experience of this order led him to the conclusion that "the final integration of neural impulses" could not be a function of the cerebral cortex, but required a deeply-seated central mechanism for its achievement.

Yet, not unnaturally, he looked to some earlier authorities on cerebral physiology for data or opinions that might point in the direction in which his thought was leading him. There is no evidence that he went back to Carpenter, but he turned to the writings of Herbert Spencer and to those of Jackson and Sherrington, and in all three sources believed that he had found ideas sympathetic to his own.

We know, of course, that neither Jackson nor Sherrington accepted mental activity as a function of nervous systems, but both had views upon the integrative function of the nervous system and of the plan upon which it seemed to be based.

Jackson was greatly influenced by the writings of that erudite Victorian sage, Herbert Spencer, and amongst his many references to Spencer in his papers, one particular passage is more than once quoted: at first in full and later in part. The fragmentary quotation is as follows: "The seat of consciousness is that nervous centre to which, mediately or immediately, the most heterogeneous impressions are brought."

Penfield also quotes this fragment in some of his papers, and regards it as pointing to, or as compatible with the existence of, his centrencephalic integrating system in the brain-stem.

The passage comes from Volume 1 of Spencer's "Principles of Psychology" (1890, p. 105), and given in full, as Jackson originally gave it (H. J. **1,** 107), it reads as follows: "It does not follow, as it at first seems to do, that feelings are never located in the inferior nervous centres. On the contrary, it may well be that in lower types the homologues of these inferior centres are the seats of consciousness. The true implication is, that in any case *the seat of consciousness is that nervous centre to which, mediately or immediately, the most heterogeneous impressions are brought;* and it is not improbable that, in the course of nerve evolution, centres which were once the highest are supplanted by others in which co-ordination is carried a stage further, and which thereupon become the places of feeling while the centres before predominant become automatic."

The fragment which Penfield quotes from this lengthy statement is here given in italics, and it is clear that, removed from its context, it gives a false

sense to Spencer's views if these are to be applied to the supposed psychological properties of a centrencephalic integrating system in man.

A similar abbreviation of Jackson's expressed views on the substrata of consciousness leads to a misinterpretation of these by Penfield.

Thus (1954*c*), Penfield writes, "The study of clinical neurology and particularly the study of epilepsy drove Hughlings Jackson to hypothecate [*sic*] the existence of an area of brain, separate from the motor and sensory cortex, in which the highest level of functional integration took place. Here there must be, he said, a final sensory and motor arrangement that formed the "neural substratum of consciousness," and he is quoted as naming the frontal cortex as the seat of consciousness (Penfield and Rasmussen, 1950, p. 235). What in fact Jackson did say (H. J. **1,** 241)[1] was as follows: "We spoke of the substrata of consciousness as being the highest nervous arrangements. Yet to avoid misinterpretation we pointed out explicitly some time back that we do not really suppose there to be one fixed seat of consciousness. Now, if the expression be permitted, we shall speak of several highest nervous arrangements. Consciousness is not an unvarying independent entity. Consciousness arises during activity of *some* of those of our highest nervous arrangements by which the correspondence of the organism with its environment is being affected. Our present consciousness is our now mental state: it is such or such according to the kind of correspondence now being affected. As this correspondence is continually changing, the nervous arrangements concerned are continually different. . . . It is an anatomical problem to discover where in the nervous system these arrangements lie which are in leading activity when we are conscious thus and thus." Again he writes (H. J., **2,** 15), "The question is, how far down in the nervous system are there psychical states during nervous activity. Is the brain the organ of mind, or only the chief part of that organ. I give no opinion on that difficult subject. . . . But were I to make an abrupt limit to the concomitance of psychical with nervous states, I should place the lower limit at the lower motor (Hitzig and Ferrier) and lower sensory (Ferrier's) centres" (that is, the pre- and post-central cortex).

All this is something very different from Penfield's attribution to Jackson of the view that "here is an area of the brain" which is the fixed neural substratum of consciousness, and one can draw from Jackson's writings nothing to favour the idea of such a fixed substratum in the brain-stem or elsewhere.

Finally, Penfield seems not to have grasped Sherrington's views on the role of the cerebral cortex as the highest level of integrative activity in respect of movements. Thus, Penfield and Rasmussen (1950), in a chapter devoted to Sherrington's findings and views on the anthropoid

[1]References to Jackson's papers are taken from the "Selected Writings," vols. 1 and 2. They are given as H. J. followed by volume and page number.

cortex (Leyton and Sherrington, 1917), in which the authors describe the movements ensuing upon focal electrical stimulation as fractional components of larger movement complexes, remark that "Sherrington and his pupils did not hypothesize where the 'organ' which has as its function the compounding of cortical movements might be situated." Yet this is precisely what Leyton and Sherrington did in the paper cited, when they wrote, "The motor cortex appears *par excellence* a synthetic organ for motor acts . . . together the two motor cortices form, in such an animal type as the anthropoid ape, an organ for the synthesis of movements—and of postures—on a vast scale." Again, they express the view that the fragmentary movements seen on cortical stimulation must under normal conditions be "within the grasp of the organ which has the varied compounding of them." The organ referred to is, quite clearly, the cerebral cortex. Finally, they say, "comparison of the synthetic activity of the bulbospinal organ with that of the motor cortex reveals an excess of synthetic capacity in the latter, as evidenced by the variety and multiform scope of the motor acts and sequences it builds up."

Nevertheless, after reviewing the Leyton and Sherrington observations on the motor cortex, Penfield and Rasmussen (p. 19) submit their own hypothesis that "the control of the synthesis of cortical motor and cortical sensory processes is to be found in the diencephalon and mesencephalon," without seeming to be aware that it runs directly counter to the conclusions that Leyton and Sherrington draw from their observations.

Thus, from the appeal to the cortical studies of Leyton and Sherrington in support of the concept of the brain-stem as the highest level of integrative activity within the brain, it must be conceded that we come away empty-handed. These observations as well as Sherrington's earlier work on the plan of co-ordination in cord and brain-stem, with its beautiful amplification by Magnus and his school, all point to the dominance of the cerebral cortex. They point also to the conclusion that the essential role of the entire nervous system is an integrative one, and provide no warrant for a belief in a special faculty of integration resident in small and scattered cell groups in the intralaminar nuclei of the thalamus or in the tegmentum of the brain-stem.

Nevertheless, there is no finality in science. Even Sherrington's "final common path" has assumed a complex character under the influence of modern physiological research, which suggests that the spinal cord may be the seat of activities hitherto unsuspected or formerly attributed to higher levels of the nervous system. Therefore, even if nothing in the history of neurophysiology up to date, since Carpenter's creation, the automatic apparatus, affords any indication that the brain-stem is the functional equivalent of Jackson's highest level, as Penfield claims (1954*c*), any new facts, and hypotheses based upon them, must be considered on their merits.

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We may ask therefore whether any new facts emerging from Penfield's observations on epilepsy require or support the new and striking concept of the integrative activity of the nervous system that he proposes, and, conversely, whether the concept as presented by Penfield generalizes the facts he provides.

In the analysis which follows, it has seemed to the writer that direct quotations from Penfield's numerous expositions of his concept are essential if his precise meaning and claims are to be fairly presented, and the general coherence of its constitutent elements is to be assessed.

(*b*) *Methods and Material*

Penfield's studies have been made mainly on the subjects of focal epilepsy, though a number of cases of cerebral tumour appear in his monograph with Rasmussen (1950).[1] The necessary surgical procedures involving the exposure of different cortical regions have been amplified by electrocorticography and by the electrical stimulation of the cortex. In many instances local cortical excisions of epileptogenic foci have also been undertaken.

Cortical mapmaking as a record of the results of the punctate electrical stimulation of the cerebral cortex has been zestfully pursued since 1870, and there are no signs that this topographical exercise evokes less enthusiasm now than at any time in this long period. Ever new excitable regions which, as a result of new stimulating instruments and new variables of stimulation, continue to be revealed have added greatly to a sort of necessary but simple functional topography of the cerebral cortex: what Jackson spoke of as the anatomy of the cortex, as opposed to its morphology. There can be no doubt that to this topography of motor and sensory functions, the vast human material which Penfield has studied over a long period of years has added many interesting and original details. Yet all such maps show the same essential features, and whether they add to *our understanding of the nature* of cortical dynamics may be doubted. As practised, this method has probably yielded its main harvest, and only an aftermath can at this time be expected. Further, how artificial these maps are as indicating the plan of motor representation, has been revealed by the recent work of Liddell and Phillips (1950) which gives us a pattern so closely corresponding to the concept of motor representation we owe to Jackson as to make it impossible any longer to justify ignorance of his fundamental contribution to cerebral physiology. Yet the familiar cortical map must reveal something inherent in the organization of movements by the cortex, even though indirectly. Possibly, the "cortical mosaic" stands in relation to the origin of the pyramidal tract and indicates the arrangement of the cells of origin of this system in the cortex.

[1]References to the monograph of Penfield and Rasmussen are given as P. and R., with page number.

There is a tendency to equate the entire precentral cortex with the cells of origin of the pyramidal system. Thus, Penfield (1954*a*) writes, "The precentral gyrus can do nothing of itself. It can only serve as a keyboard upon which the patterned stream of voluntary impulses plays" (p. 291).

This may be a mistaken paraphrase of a sentence in a paper of the present writer, which Penfield has quoted (1954*b*), where it is said, "The pyramidal system of itself initiates nothing, and to speak of it as responsible for this and that category of movement is to ignore the source and motive power of its activities . . . Willed movement is activated by controlling afferent patterns of excitation" (Walshe, 1947).

But what may be true of the pyramidal system can hardly be transferred to the precentral cortex, as Penfield here appears to do.

In short, the method of electrical stimulation of the cortex bears no resemblance to any normal influence to which the cortex is subjected; that is, it is not an adequate stimulus in Sherrington's sense, and we have no grounds for assuming that what it yields bears a direct resemblance to the action of the cortex in the intact organism, when we are not interfering with it, either therapeutically or experimentally (cf. Walshe, 1951).

Further, the cortical map necessarily gives an impression of stability of response that we know is illusory. It is a "still," failing to fulfil the functions of what is really a "moving" picture. This limitation of the map applies even more to the "homunculus" that Penfield has introduced into neurological iconography. Those able to read do not need this aid, which in its nature is a kind of reversion to mediæval heraldry: an art necessitated by the illiteracy of the Middle Ages, but rendered attractive by the skill of contemporary artists. The modern "homunculus" has no such artistic merits as the heraldic monster and, indeed, its most severe critic is Penfield, who says of it, "such drawings may easily become confusing if too much significance is attributed to the shape and comparative size. This is corrected by the underlying indication of extent of representation." This is truly a destructive criticism since the shapes and relative sizes of these drawings provide their sole *raison d'être*.

It has been necessary to go into these points at some length, since the pith of Penfield's hypothesis lies in his interpretation of the motor responses to cortical stimulation.

There remain two orders of response noted by Penfield that, in his view, stand apart from the ordinary motor responses to electrical stimulation; these are "vocalization" and, occasionally noted in chronic epileptic subjects only, what appear to be memory recalls.

Finally, there are the monoplegias and hemiplegias ensuing upon surgically indicated cortical excisions. No description of these is anywhere given, but from them also Penfield draws some inferences germane to his hypothesis.

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(*c*) *The Morphology of the Centrencephalic System*

Data as to the morphology of this system have developed very little over the years. In his original (1938) paper, Penfield goes no further than to say that "there is much evidence of a level of integration within the central nervous system that is higher than that to be found in the cerebral cortex, evidence of a regional localisation of the neuronal mechanism involved in this integration. I suggest that this region lies not in the new brain but in the old . . . probably in the diencephalon." In 1949, he still refrained from a more precise localization, but said the system's boundaries "might extend a little way into the pons or possibly a little way upward beyond the thalamus." Shortly after this date, Magoun's papers on the reticular activating system (1950) began to appear, and in 1953 at the Laurentian symposium, Penfield said, "it may be suggested at once that the intralaminar system of the thalamus and the reticular formation of the brain-stem and the non-specific projection systems which have widespread connexions with the cortex of both sides satisfy the definition. These doubtless constitute a beginning of anatomical knowledge of the centrencephalic system" (1954*a*). Thus, the centrencephalic integrating system is now postulated as located within Magoun's reticular activating system, but it may not be assumed that the conclusions as to the functions of this system, which Magoun has drawn from his animal experiments, conform to those postulated by Penfield for his centrencephalic system in man. Olszewski (1954) has pointed out that morphologically the *formatio reticularis* of the brain-stem does not correspond to the reticular system of the physiologists, and that its connexions are largely unknown. It is not a morphological unity, but a collection of nuclei of very different structure, and he says that "an effort to correlate physiological observations with the arrangement of nuclei and fibre tracts of the lower brain-stem should prove much more fruitful than the present practice of regarding the reticular formation as an anatomical entity." It may be added to this that the intralaminar nuclei belong to the dorsal thalamus, not to the ventral thalamus, and are therefore phylogenetically distinct from the formatio reticularis or the hypothalamus. It seems clear, therefore, that the morphology of the centrencephalic system is not fully clarified by identifying it with that of the reticular activating system. Magoun himself agreed (1954) that rostral to the mid-brain there is no clear evidence of the precise morpology of this system.

Finally, in respect of the so-called non-specific projections said to have widespread cortical connexions, Nauta and Whitlock (1954), as a result of an anatomical study, state that there is little decisive information regarding the anatomical substratum for widespread neocortical transmission of non-specific thalamic activity.

Walther Riese (1950) has remarked that structures are but facilities for function, but of necessity function demands these facilities, and Brodmann,

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in the concluding passage of "*Vergleichende Lokalizationslehre der Grosshirnrinde*" (1909), reminds us of this when he says, quoting Bernhard Gudden, "Any physiological conclusion that is incompatible with an established anatomical fact is meaningless. First, therefore, let us have anatomy and then physiology, but if physiology is to come first, then see that it has its anatomical substratum."

The history of cortical cytoarchitectonics might, perhaps, warn us against laying too much stress upon histological studies, for undoubtedly a slavish adherence to that scheme of cytoarchitectonics which postulated a cortex of 200 "organs" for a period cramped physiological thinking (cf. Walshe, 1942). Yet this was because the histology was unreliable, and thus Gudden's postulates are not invalidated. On the other hand, Head and Rivers' concept of protopathic and epicritic afferent systems was an example of speculation concerning function which came to grief from neglect of Gudden's postulate, for not only did the necessary structures prove wanting, but the proposed distribution of functions between them was in its nature incoherent.

(*d*) *The Functions of the Centrencephalic System and those of the Cerebral Cortex in the Integrative Action of the Nervous System as a Whole*

Before giving detailed consideration of the functions attributed to the centrencephalic system, a brief summary of what is claimed for it is appropriate. Penfield represents it as being (1) "a centre for conscious thought"; "the place of understanding", and (2) "a sensorimotor centre"; the highest and the final level of neural integration.

How inseparable these psychological and physiological functions seem to him is indicated in the following passage (1951): "Skilled finger movement, like that of a pianist, can only be elicited from the precentral gyrus when it is played upon by well-integrated impulses that come to it in a normal manner from some source within the brain that is functionally higher than the convolution itself. When he begins to play, the pianist does so with both hands and it would seem that only from the upper brain-stem could come the directing impulses that cause the fingers to move across the keyboard, so skilfully reproducing the melody. This is not a reverberating circuit, but a discriminating series of impulses to the cortex. Thus, I am suggesting that the master motor area, in the brain of man, may be found at the level of the higher brain-stem where sensory information of finger position is available, where the visual image of the piano is available, where the memory of the music is available, as well as the auditory effect, and were conscious control is exerted upon the mechanisms of movement. Such a master mechanism must contain a sensorimotor complex as well as a complex for conscious thought." It might indeed seem from all this that no major function remains for the cerebral cortex, and Penfield and Rasmussen do in fact suggest that a large

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proportion of it is "dispensable," though not without function, but "employed by the individual on an optional basis" (P. and R., p. 201).

Thus we see clearly revealed the vast scope of the concept that we are to examine in detail.

(*e*) *The Results of Penfield's Electrical Stimulation of the Precentral Gyrus and the Inferences Drawn Therefrom*

Penfield places the movements he thus evokes in two categories: (1) *Limb movements*. These are variously described, as being like the movements of the newborn child and infant, as resembling the movements of an epileptic convulsion, and also as resembling the muscular contractions evoked from anterior horn cell stimulation. Again, they are described as crude or simple movements of flexion and extension at one or more joints. It is difficult to accept that these electrically evoked movements can resemble such diverse and widely dissimilar phenomena, but it appears that, for the purposes of the concept of the centrencephalic system, the important analogy is that with infantile movements. (2) The second group, attributed to the activity of "inborn neuronal connexions," includes such bilateral movement complexes as *vocalization*, *swallowing*, etc. These are spoken of as "skilled"; surely a misuse of a word customarily reserved for learned movements, and meaningless in any other sense.

From this description and classification Penfield draws the following inferences: that electrical stimulation and epileptic discharge yield evidence of the representation in the precentral cortex of infantile type movements only. A number of reasons are given for this state of things: that electrical stimulation does not provide integrated impulses, that the impulses thus engendered pass straight into the pyramidal system and down to the cord without entering the centrencephalic system, and finally (and this applies to integrated impulses reaching the precentral gyrus in the normal way from the centrencephalic system) that the precentral gyrus "can of itself do nothing. It can serve only as a keyboard upon which the patterned stream of impulses plays" (Penfield, 1954*a*). It is only a "way station" for the discriminative stream of "well-integrated impulses" that reach it from the centrencephalic system, and the elaboration of manual skills is not a function of this gyrus but, as will appear, of "elaborating fields" in other cortical regions which act by two-way paths connecting them with this system.

As regards the bilateral movement complexes (vocalization, swallowing, sucking and, presumably, though they are not mentioned, sneezing and yawning), Penfield believes that here we are dealing with co-ordinated processes of a higher order than the limb movements, and he notes that while electrical stimulation of the precentral cortex appears to "paralyse" skilled movements of the limbs, it activates these axial muscle "skills." He explains this differential behaviour by the suggestion that "vocaliza-

tion, swallowing and salivation have migrated out to the cortex of man in the Rolandic convolutions" (P. and R., p. 60).[1]

The basis of the hypothesis of "migration" appears to be the failure of Sherrington, using faradic stimuli and general anæsthesia, to evoke vocalization from the anthropoid. Yet Penfield states that he also failed to evoke it in the human subject by these means, and succeeded in doing so only when the thyraton and Rahm stimulators came into use in 1935, and under local anæsthesia.

It would seem as well to ascertain whether or not these stimulators used under identical conditions are able to evoke vocalization in the usual run of vocalizing animals used in experimental neurophysiology before postulating this migration.

As for the specific differences postulated between limb movements and vocalization, etc., we know that when evoked by electrical stimulation of the anthropoid cortex, limb movements may involve many muscles, and Sherrington has described primary, secondary and tertiary movements in these circumstances. These movements display reciprocal innervation, which is an integral element in co-ordination. In what respect are vocalization, swallowing, etc., in a different category? Surely only in that the muscles employed are more widely distributed. The only difference is a topographical one. Again, if vocalization be, as Penfield suggests, the same in the infant and in the epileptic cry, how can a high order of co-ordination or of skill be postulated of it?

It would seem, then, that this distinction has no substance, and that no data are offered that would allow us to postulate a special migration of representation of these bilateral movement complexes from brain-stem to cortex.

To summarize.—The proposal is that electrical stimulation of the precentral cortex (like epileptic discharge from this cortex) evokes movements having the essential quality of the movements of the infant, and provides no indication that acquired movement-complexes are represented in this cortical region. The explanation is that the impulses set up in the precentral cortex in these circumstances have not already been integrated in the centrencephalic system, and, since they travel down in the pyramidal tracts to the cord, they do not subsequently enter this system. The precentral cortex itself has no power of integrating impulses.

It is here submitted that these conclusions do not arise from the facts of observation, because we cannot draw refined physiological conclusions directly from the results of so unphysiological a procedure as the electrical stimulation of the cortex, and also, because as a matter of simple observation it is not possible to accept that the movements electrically evoked in

[1]Elsewhere (1954*a* and *d*) Penfield describes these movements as mediated by subcortical mechanisms and activated at a distance by cortical stimulation.

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this way resemble either the movements of an infant or those of an epileptic fit. *Naïvely interpreted*, electrical stimulation of the precentral cortex throws no direct light upon the dynamic properties of this cortical region. In Jackson's words, it tells only about the "anatomy" of the precentral gyrus.[1] Certainly the observation of these movements does not reveal the existence, or suggest the necessity, of a centrencephalic integrating system.

(*f*) *The Results of Penfield's Electrical Stimulation of the Postcentral Cortex and the Inferences Drawn Therefrom*

The character of the sensations evoked in this way is said to be crude and elementary, whether visual, auditory or somatosensory modes are in question. When the visual cortex is stimulated what are experienced by the subject are colours or simple lights, "there is no concept [*sic*] such as a horse or a flower or a football" (P. and R., p. 208).

From this Penfield concludes that the primary sensory representations are merely "stop-overs in the afferent stream of sensory impulses." These impulses originate exteroceptively, proprioceptively, in the eye or in the ear, and then "pass through these cortical representations on their way to a higher neuron level . . . from cortex to diencephalon the stream is still afferent" (P. and R., p. 232). Integration takes place in the brain-stem.

Strangely, unlike impulses engendered by stimulation of the precentral gyrus, those evoked from the postcentral gyrus are said to pass through the centrencephalic system (Penfield, 1956). Nevertheless, the sensations evoked remain crude like the motor responses. But the crudity of the latter is ascribed to their not passing through the centrencephalic system. Here is a curious discrepancy of behaviour in the light of what is postulated of sensory impulses when they enter this system, whether normally or upon electrical stimulation of the cortex.

The explanation probably is that we do not and cannot know whether either category of impulse electrically evoked enters a system in respect of which, so far, no conclusive evidence of existence has yet appeared.

(*g*) *What Roles Remain for the Primary Motor and Sensory Representations?*

The student of this hypothesis cannot find it easy to accept the extreme downgrading in the neural hierarchy proposed for the precentral and postcentral gyri and for the other primary sensory regions of the cortex.

[1]Jackson's use of the term "anatomy" should be recalled. Thus, "The anatomy of the nervous system must be carefully distinguished from its morphology. Morphology deals with the sizes, shapes and topographical relations of nervous masses. Nervous anatomy deals with centres, that is, with regions of the nervous system as they represent parts of the body. The morphology of the Rolandic area was well known before the researches of Hitzig and Ferrier; but until their experiments, nothing was known of the anatomy of these parts. Physiology deals with the dynamic activities of neurones" (Summarized from "The Selected Writings," Vol. I).

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He will remember that the motor cortex has been described by Sherrington as "*par excellence* a synthetic organ for motor acts," and, acting with its fellow, "an organ for synthesis of movements and postures on a vast scale." In its new role it can scarcely be regarded as a representation in any sense. It has become a way-station only, a passive keyboard played upon by higher levels.

The fate of the primary sensory regions is comparable, and they are but way-stations on afferent paths that dip down from the cortex to reach their terminus in the brain-stem.

In one of his latest pronouncements (1956) upon this matter, Penfield leaves us in no doubt that his view of the roles of the sensory and motor cortical regions differs essentially from views hitherto held when he says, "the sensory areas of the cortex are no more than way-stations in the several currents that carry different forms of sensation into the centrencephalic integrating system, and the cortical motor areas are way-stations in the stream of outflowing impulses that produce motor activity." We must regret that the metaphor of the "way-station" is the most precise statement that Penfield can make about the dynamic activities of these cortical regions. The term is not an adequate substitute for a physiological description.

And yet, paradoxically enough, as Penfield allows, all the functions hitherto attributed to these two regions are abolished when they are destroyed; functions which, as he concludes from his stimulations, "do not seem to be represented there."

What are the data of observation proposed by Penfield in support of this rejection of former physiological views, and what the explanation of the paradox?

The only *factual* datum so far offered is the form of the movements evoked by electrical stimulation of the cortex. These are not like the purposive movement complexes seen in normal adults; the acquired skills. Upon this single observation, which in fact is an extremely old observation both for man and for animals, the entire edifice of the hypothesis, as far as we have yet examined it, has been built. An inference is drawn as to the physiological significance of electrically evoked movements, a fallacious one, it is here suggested, and from this the remaining inferences have in their turn been derived. This is a very inconsiderable foundation upon which to construct an hypothesis, the acceptance of which would involve the rejection of teachings that have long been accepted and that still appear to rest upon sound observational foundations.

It remains to be seen how the paralysing consequences of destroying the precentral and postcentral gyri arise, since their functions, as these have been understood, are no longer allowed them by Penfield.

Where are these functions now to be sought? The answer is, in

certain "elaborating fields" in the cortex: cortical regions which mediate "hand skills" and "picture skilful acts."

(h) The Elaborating Regions of the Cortex and Their Functions

These regions are not in direct intracortical connexion with one another or with the primary motor and sensory regions, for it is assumed that intracortical association fibres play no role, though Penfield, in a single reference (P. and R., p. 211), allows them to unite the precentral and postcentral gyri. Relations between these different cortical "mechanisms" are achieved by a direct to-and-fro connexion with the centrencephalic system. Thus each elaborating region is connected by a two-way path with its "corresponding department" of this system. In this way only, the isolated cortical mechanisms are enabled to play their parts in the activity of the different departments of the centrencephalic system, while "the cortical projections serve to elaborate afferent and efferent mechanisms."[1] It is in this way that the frontal cortex "serves the purpose of elaboration of certain forms of thinking." Nevertheless it is "within the diencephalon (that) there are neurone circuits which may be considered the highest level of neuronal representation and re-representation." Here in this last sentence we meet the terminology of Jackson, but not the teaching.

This complex series of shuttle pathways between cortex and centrencephalic system are not yet morphologically identified, though by some electro-physiologically suspected to exist.

We are at some disadvantage in considering the role of the elaborating "mechanisms" in the cortex, for the term "elaboration" has no fixed scientific connotation in physiology, and it is nowhere defined by Penfield. It can hardly have the same references as the terms "integration" or "co-ordination," for were that the case, Penfield would surely have used one or other of them, and would not have been forced again to use a non-specific term from outside the grammar of physiology.

The unspecified process of elaboration is carried out by "mechanisms" in the cortex, as follows: (1) In the anterior frontal lobe are mechanisms for thinking and the elaboration of thought, and for the elaboration of hand skills. (2) In the parietal region is a mechanism, called "the acquired mechanism for the extremities," which elaborates hand and foot skills and "pictures the skilful acts carried out by hand and foot."

It has to be added that these elaborating mechanisms are all duplicated; one of each of them in each hemisphere, except the elaborating mechanisms for speech, which are found only in the dominant hemisphere (*v. infra*, p. 531). Thus, the skills of one hand are represented in each hemisphere, and so for the other limbs. Further, each of these mechanisms acts

[1]This sentence is from the closing paragraph of Penfield and Rasmussen's monograph of 1950 (p. 235), but the present writer confesses that he cannot conceive how a projection can elaborate a mechanism.

bilaterally through its connexions with the centrencephalic system in the brain-stem.

A sentence in which the anterior frontal elaborating mechanism for thought is said to be "employed" by the centrencephalic system, reveals the relationship between these cortical mechanisms and the centrencephalic system postulated by Penfield.

Thus, even these cortical mechanisms remain essentially subordinate to the centrencephalic system, which "employs" them "on an optional basis" according to the activities of the moment. Unless thus summoned to action the cortex is not employed, but when employed it "makes possible and elaborates" the functions of the centrencephalic system. Here again, we labour once more under the handicap that general statements of this order in non-scientific language do not convey physiological knowledge.

Penfield, in a most revealing passage, describes what appears to be the hypothetical case of a boy of 6 who, sustaining a destroying lesion of his left frontoparietal cortex, is left with a permanent right hemiplegia, and he interprets this case, in the light of his hypothesis, as exemplifying the relation of the precentral-postcentral strip to the elaborating mechanisms of the cortex as he conceives this.

The child soon re-learns, he tells us, to vocalize, articulate and speak in virtue of his "newly employed right-sided frontal areas of speech elaboration" (*v. supra*, p. 530) but his right arm is totally paralysed and he is unaware of its position unless he looks at it. Here follows a most remarkable passage, "because of the almost completely exclusive representation of movement and sensation in one hemisphere it will remain practically useless for life. But the skilled patterns of that hand are not destroyed. The left hand loses none of its skill, and furthermore it very soon takes over the complicated performances which were previously allotted to the right hand, such as playing the treble part on the piano. This is possible because the fields of elaboration of hand action are bilateral. They are not localized in the sensorimotor convolutions of one side . . . the destruction of the elaborative fields for the hand on one side mattered little to him for they were bilateral, and the left hand inherited the skill of the right" (P. and R., pp. 222–3).

How all this can be said to matter little to the child is obscure, for, after all, his right arm is destined to remain paralysed for life, whatever may be assumed about the preservation of the "patterns" of its skills, and in what sense can the precentral gyrus be said to have the "almost exclusive representation of movements," if, what is the same thing, the patterns of motor skills are represented elsewhere and bilaterally?

What it is not possible to understand is how, on this hypothesis, the limb is paralysed at all. *Ex hypothesi* it is still in neuronal connexion through the centrencephalic system with the patterns of its skills in the

intact hemisphere. The relations of one hemisphere with its fellow are mediated through this centrally placed, bilaterally acting, brain-stem integrating system, wherein, as we have seen, are available and fully integrated every mode of sensibility, and whence fully integrated voluntary impulses descend to the cord.

It is, in fact, impossible for a limb to be parted from one of its duplicated elaborating fields and the centrencephalic system as a result of any cortical lesion in one hemisphere, according to this hypothesis. Nevertheless, the boy has a hemiplegia and it is possible to account for it on two grounds only: (1) that after all, and as we have always supposed, the sensorimotor representations in the pre- and post-central gyri do mediate skilled movements of the crossed limbs, and (2) that such special bilaterally acting elaborating fields for acquired skills, as are here postulated, have no existence.

Perhaps the final claim that the left hand does not learn, but simply "inherits" the skills of the right, is an appropriate ending to a sequence of speculations that, in effect, end by negativing the validity of the proposition they set out to prove. In short, this exposition of his hypothesis by Penfield is not free from some confusion of thought.

To summarize all that has gone before concerning the relationship of the cortex to the centrencephalic system, we find that the primary motor and sensory representations have been physiologically downgraded to the status of "stopovers" on sensory and motor paths, with no role in the integration of sensation or of movement. Their place appears to be taken primarily by the centrencephalic system with its elaborative appendices in the cortex, the system remaining the highest level of neuronal "representation and re-representation."

Different cortical regions are not interconnected by intracortical, or apparently by cerebral association paths beneath the cortex, but are isolated from one another, and are related only by means of direct paths between each cortical region and the centrencephalic system.

The conclusion here submitted is that these views rest upon no sound basis of observation, that the very exiguous data offered neither require nor tolerate this complicated speculation, and provide no conclusive evidence of the existence of a centrencephalic integrating system in the brain-stem.

(*i*) *The Temporal Lobe and the Centrencephalic System*

The functions of the temporal lobe in its close relations with the centrencephalic system are believed by Penfield to have been revealed by some of his own observations which are described by him as no less important than Fritsch and Hitzig's discovery of the excitability of the cortex (Penfield, 1952).

In his hands, electrical stimulation of certain regions of the temporal

cortex may evoke memories, and "seems to recreate specific experiences from the past in a manner accepted by the patient as authentic," and so that he "is made aware of everything to which he was paying attention during a specific interval of time" (Penfield, 1956). As to this, we have no means of verifying whether the past experience the patient claims to have recalled is "everything" to which he was paying attention at the relevant time, or to what degree his "recall" is a faithful or complete replica of that past. He cannot know this himself. Moreover, we note that, unlike the excitability of the cortex discovered by Fritsch and Hitzig which is a property of every cerebral cortex duly stimulated, this result is an occasional one restricted in its occurrence to some subjects of temporal lobe epilepsy, and not to all of these.

This unpredictable and occasional incidence may seem to remove the phenomenon from the category of responses to stimulation with which we are familiar, and may raise difficulties of interpretation even greater than those that surround the interpretation of movements on cortical stimulation.

These "memory recalls" are unique in another sense. Thus, they are evocable from the cortical grey matter but not from the subcortical white matter (Penfield, 1954A, p. 306), being in this unlike the sensory and motor responses to cortical stimulation. In view of what Penfield believes to be the process by which these memories are recalled, this discrepancy is hard to account for, since, as he says, "I have imagined that the steady pressure of impulses applied by the electrode to the temporal cortex causes one synaptic barrier after another to open for the passage of the current, slowly, steadily, in a pattern that was established by the effect of the impulses delivered to the temporal cortex from the centrencephalic system at the time of the original experience" (p. 302).

In the same communication, Penfield sums up the role of the temporal cortex as the repository of memories in the following terms: "the hypothesis is suggested that sensory information is integrated within the centrencephalic system. A selected portion of this information is then somehow projected onwards to the temporal cortex by that portion of the system which is in functional connexion with the temporal cortex of both sides. As it is thus projected, a comparison is made with past experiences, thanks to the records of the past that are held there, and judgment with regard to familiarity and significance is made. There must then be re-projection back to the centrencephalic system by means of the same neurones that are activated by the surgeon's electrode. A plan of action is then formulated. This formulation would also seem to be carried out by means of ganglionic activity in the centrencephalic system because of the fact that the activating stream of motor impulses is sent out from that system" (loc. cit., p. 303).

The temporal cortex is likened to a filing cabinet for memories where

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they are stored in a continuous lifelong record, which is compared with a strip of cinema film or a tape recorder, and true to the general mechanist tone of the hypothesis the temporal cortex becomes the seat of various "mechanisms"; mechanisms for judgments, mechanisms for dreams, mechanisms for memories, each with its own tract to the central switchboard to which Penfield compares the centrencephalic system.[1]

The fact of clinical observation that memories are not lost as a result of unilateral destroying lesions of the temporal lobe is accounted for by Penfie'd by proposing that every memory record is duplicated, each experience being recorded in both hemispheres. But *this* is not a fact of observation, it is merely a supposition to account for a fact of observation. His argument may be fairly stated thus: memories are not lost from a unilateral lesion because they are laid down on both sides: they must be laid down on both sides because they are not lost with a unilateral lesion. This is the argument in a circle. There is no clinical evidence of a duplication of memory records.

The only relevant clinical fact is Penfield's observation of experiential recalls on stimulating the temporal cortex of some subjects of temporal lobe epilepsy, and whether this must be interpreted as localizing memories in the normal temporal cortex can hardly yet be a matter for positive pronouncements.

For what homology may be worth, it may be recalled that Lashley's experiments did not afford evidence that memories are laid down in the temporal lobe in animals, and he concludes that we do not know the nature or location of the memory trace (Lashley, 1950).

IV. Conclusion: The Role of the Centrencephalic Integrating System and the Evidence of its Existence

In a general theory containing so many constituent elements, or perhaps it should be said, involving the postulation of so many elements, it is not easy as we read its many expositions to keep in mind what are the data of observation and what the inferences.

Let us take, for example, a passage concerning the temporal lobe from a recent paper (Penfield, 1956) where we read: "The pattern of each successive experience is somehow projected from the centrencephalic system outward to the temporal cortex on the two sides (including the hippocampal regions perhaps) in a continuous flow that is interrupted only by deep sleep or by coma. It would seem that the projection could

[1]How widely the localizers of memory and mind may vary in their choice of locations is exemplified by some expressed conclusions of Nielsen (Hixon Symposium, 1951, p. 277) to the effect that "We have two kinds of knowledge: the simple cognitive knowledge—the accumulation of facts; and the other kind—the knowledge of what to do with facts. The latter is stored in the frontal lobes. From area 6 back is factual knowledge; from area 6 forward is wisdom."

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only come from this central integrating area, since it is there and only there that all sensory and psychical elaborative circuits converge."

Of these two sentences, the first is plainly hypothetical in all respects. It is based upon the second sentence which makes a categorical pronouncement that all sensory and psychical elaborative circuits converge in the centrencephalic system. But this also is hypothetical, and one hypothesis cannot prove the validity of another. We see here an example of the almost insensible transformation of hypotheses into statements of fact.

Again, let us take an example from what purports to be a consideration of the problem of voluntary movement "on a physiological basis" (Penfield, 1954*b*). "It is obvious," he says, "that the nature of voluntary action is determined according to sensory information, but also according to the guidance of memory and the conclusions of reason." We find ourselves already with one foot, as it were, in the territory of psychology, but he continues, "This means that there must be a neural mechanism within the central nervous system capable of producing complicated integration before the appropriate motor impulses are delivered to the precentral gyrus."

If he had said here "pyramidal tract" instead of "precentral gyrus" the suggestion would have been arguable, for is not the precentral region, as far as clinical and experimental observation indicates, and as we have already recalled in this article, an organ for the synthesis of movements and of postures? How, then, may we state that voluntary impulses *must* have been integrated in the brain-stem prior to the involvement of the precentral gyrus in their organization? We may make no such assumption. Again, he says, "One conclusion in regard to the origin of these patterned impulses may be established at once. They do not come directly across the neighbouring cerebral cortex," because, he adds, ablation of cortex frontal to the precentral gyrus, or of the postcentral gyrus behind it, does not abolish voluntary movement.

Therefore, the thesis runs, the impulses must flow to the cortex from some subcortical source, pass thence through the precentral gyrus and then descend again to the bulbospinal grey matter.

It is here strongly submitted that this sequence of events is not established, and its occurrence is not compatible with the known results of lesions of the postcentral gyrus as these affect skilled movement complexes. These movements are grossly disordered by the absence of normally presented patterns of afferent excitation which the precentral cortex received from the postcentral cortex, and doubtless also from other cortical regions. Upon all this, Penfield's comment is that "the act is not abolished, although it may become awkward." Surely, this is a very misleading meiosis.

Moreover, Penfield himself (P. and R., p. 211) maintains that the precentral and postcentral gyri, the "sensorimotor strip" as he calls it,

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act as a unit, that the two gyri are closely related by "a succession of nerve circuits" which pass through these paired gyri. How, then, can he also maintain that there are no intracortical relations between them?

In other words, the proposition that voluntary motor impulses are already fully co-ordinated, or integrated, in the brain-stem before they reach the precentral gyrus, that the postcentral sensory cortex plays no role in this co-ordination, is indeed a speculation based upon three prior suppositions: namely, that the precentral gyrus is no more than a way-station with no integrating functions, that the postcentral gyrus is also merely a way-station on the afferent path from sense organ to centrencephalic system and has no co-ordinating role, and finally that intracortical association fibres are structures without function.

In short, three structural and functional entities have had to be disallowed their hitherto accepted roles, before it becomes "reasonable"—in the phrase of Trotter which has been quoted—to postulate a brain-stem integrating system, psychological and physiological, with a series of elaborating mechanisms in the cortex as its appendages.

The primary inference with which this long sequence of hypotheses began has been discussed earlier in this article (p. 529).

Thus, the only truly factual data upon which the entire concept rests are found to be movements seen and sensations reported when the cortex is electrically stimulated. Although great numbers of human cortices were stimulated and vast numbers of motor and sensory responses recorded over the years, yet, in fact they comprise only two different data, electrically evoked movements and sensations. Upon this small base, and upon an unwarranted inference drawn as to the physiological meaning of these movements and sensations, the vast inverted pyramid of hypothesis insecurely rests.

In summary the intralaminar nuclei of the thalamus and the scattered cell masses of the formatio reticularis are said to contain a mechanism to which all varieties of sensory impulses converge, and where they are integrated to produce the results we saw described in the passage quoted on page 525 of this article. In this mechanism all motor impulses are organized. Indeed, they are assumed to arise here, presumably owing their organized character to the integrated sensory afflux which shares the system with them, and they are then "delivered" to the precentral gyrus through which they pass to no obvious purpose, making a loop downwards again to the bulbospinal grey matter and thence descending the spinal cord to the final common path.

Present also in these nuclear collections is a centre for conscious thought, coterminous, apparently, with the sensorimotor mechanisms. The complications of this system are not yet exhausted, for by two-way paths to a series of elaborating "mechanisms" in the cortex, the system is

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enabled to "work," nevertheless remaining the highest level of neural function.

It seems scarcely credible that within this small and phylogenetically ancient part of the brain such numerous and complex functions could be carried out. How comes it that despite the great development of the cerebral cortex in man, the gamut of physiological and psychological activities characteristic of man, should still be carried on in these meagre collections of cells in the "old brain," as Penfield says?

Lashley (1952) raises this last question, proposing what he calls a basic principle of neuropsychology: namely, "that the neurological activity in a psychological event cannot be simpler in structure or in number of elements than the psychological activity which it constitutes. This may be called a rule of formal isomorphism in the mathematical sense of that term. It precludes any concept of a center of consciousness as a limited centre where information is accumulated, for the complexity of mental processes is far too great to be represented by the permutations of a small number of cells. Such a centre might act as a pace-maker but not as an organizer or terminal receiver."

Jackson expressed the same point of view much more succinctly, in respect of movements, with the expression, "the more movements the more grey matter," and when we think of the large area of the motor cortex from which thumb-index movements may be electrically evoked, the burden imposed by Penfield's concept upon the *formatio reticularis* and the intralaminar thalamic nuclei appears fantastic.

The conclusion reached, therefore, in this review is that the concept of the centrencephalic integrating system lacks the support of adequate observational data. That this conclusion has been previously suggested is evident from the "General Discussion" in the Laurentian Symposium of 1953, published in the volume entitled "Brain Mechanisms and Consciousness" (1954), especially in the contributions of Lashley and of Bremer, and also in other papers of these authors (cf. Bremer, 1955).

One other possible weakness in the concept may be mentioned, not for the sake of criticism only, but to draw attention to a feature in the various papers upon the centrencephalic system which is scarcely acceptable in scientific expositions: namely, the employment as operative terms of words of common usage that have no recognized scientific reference. Examples of these have been given. Thus, the description of the precentral cortex as a "way-station" and of the postcentral cortex as a "stop-over," the suggestion that the "individual" uses his cortex "on an optional basis," the undefined term "elaboration," the statement that "selected information" is "somehow projected" to the temporal cortex, are all examples of expressions that tell us of no known neural processes and convey no physiological knowledge. It is difficult to believe that a

writer who calls the postcentral gyrus a "stop-over" can have a clear idea in terms of neural process of the role played by that cortical region.

It is submitted that this vague vernacular language is forced upon the author because he lacks the material of a scientifically based and constructed hypothesis, and has therefore to use non-scientific terminology of this order. That its adoption should have been found necessary lends support to the conclusion already reached on other grounds that scientific data and ideas adequate to demonstrate the existence of the centrencephalic system, as postulated, do not exist.

Finally, this paper began with an account of Carpenter's automatic apparatus, and it may fittingly end with the briefest possible comparison between it and its successor, the centrencephalic system.

It was submitted that Carpenter's hypothesis was the fruit, not of observation but of ratiocination, and that it was conceived in the darkness of the current ignorance of the functions of the cerebral hemispheres.

In contrast, Penfield's concept takes too little account of the harvest of a century's labours in the field of cerebral physiology. It tacitly, yet completely, rejects the view of the role of the motor cortex in the control and synthesis of movements and postures, and the concept of the entire nervous system as integrative in function, that Sherrington postulated. It ignores what clinical neurology has taught us of the activities of the sensory cortex and of the parietal cortex posterior to it. Of all this Carpenter knew nothing. Penfield may be said to have by-passed it and thus to have produced a speculative hypothesis that is virtually a replica of Carpenter's and that might have been formulated a century ago. Only in its modern vocabulary, psychological, physiological and vernacular, does it differ from Carpenter's, and as we read it we find ourselves back in the intellectual climate of mid-nineteenth century pre-Jacksonian imaginings.

The cerebral cortex, of course, could not be wholly ignored, but it is perhaps not unfair to say that it has been stretched upon the Procrustean bed of a preconceived centrencephalic system, so that we scarce can recognize it.

REFERENCES

BREMER, F. (1955) *Acta neurol. belg.*, **55,** 947.

CARPENTER, W. B. (1853) "Principles of Human Physiology." 4th Edn., London.

JACKSON, J. H. (1931) "Selected Writings" 2 Vols. London.

LASHLEY, K. S. (1952) *Proc. Ass. Res. nerv. Dis.*, **30,** 529.

—— (1954) *In* "Brain Mechanisms and Consciousness" Oxford, pp. 422 and 495.

LAYCOCK, T. (1860) "Mind and Brain, or the Correlations of Consciousness," 2 Vols. London.

LEYTON, A. S. F., and SHERRINGTON, C. S. (1917) *Quart. J. exp. Physiol.*, **11,** 135.

LIDDELL, E. G. T., and PHILLIPS, C. G. (1950) *Brain*, **73,** 132.

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MAGOUN, H. W. (1954) *In* "Brain Mechanisms and Consciousness." Oxford, p. 1.
NAUTA, W. J. H., and WHITLOCK, D. G. (1954) *In* "Brain Mechanisms and Consciousness." Oxford, p. 81.
O'LEARY, J. L. (1956) *Arch. Neurol. Psychiat., Chicago*, **76,** 187.
OLSZEWSKI, J. (1954) *In* "Brain Mechanisms and Consciousness." Oxford, p. 54.
PENFIELD, W. (1938) *Arch. Neurol. Psychiat., Chicago*, **40,** 417.
—— (1951) C. R. IVth International Cong. Neurol., 1949, Paris, **3,** 425.
—— (1952) *Arch. Neurol. Psychiat., Chicago*, **67,** 178.
—— (1954*a*) *In* "Brain Mechanisms and Consciousness." Oxford, pp. 284 and 489.
—— (1954*b*) *Brain*, **77,** 1.
——, and JASPER, H. (1954) "Epilepsy and the Functional Anatomy of the Human Brain." London.
—— (1954*c*) Proc. XIVth Internat. Cong. Psychology, Montreal, p. 47
—— (1956) Smithsonian Report for 1955, Publication 4247. Washington, D.C.
——, and RASMUSSEN, T. (1950) "The Cerebral Cortex of Man." New York.
RIESE, W. (1950) "Principles of Neurology." New York.
SCHÄFER, E. A. (1900) "Textbook of Physiology." Edinburgh, Vol. 2.
SPENCER, H. (1890) "Principles of Psychology." 3rd edition, Vol. I, London.
TROTTER, W., and DAVIES, H. M. (1913) *J. Psychol. Neurol., Lpz.*, **20,** Ergänzungsband, p. 102.
WALSHE, F. M. R. (1942) *Brain*, **65,** 409.
—— (1947) *Brain*, **70,** 329.
—— (1951) *Brain*, **74,** 249.
—— (1956) *Brain*, **79,** 529.

SARCOIDOSIS OF THE NERVOUS SYSTEM

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INTRODUCTION

SARCOIDOSIS is a relatively uncommon affection, but it has attracted a good deal of attention, partly because its ways of presenting are so diverse, and partly because its ætiology is still a puzzle. That the nervous system may occasionally be attacked has been known for about fifty years, and according to Salvesen (1935) the earliest reports were those of Winkler (1905), Boeck (1907), Mazza (1908), and Urban (1910). In addition, in 1909 Heerfordt described the clinical entity which he called "subchronic uveoparotid fever," which has come to be generally accepted as a sarcoid variant since the work of Bruins-Slot and his colleagues (1936, 1938), Pautrier (1937), and Longcope and Pierson (1937). It is interesting to note that all of Heerfordt's own original cases had neurological complaints, and so had two further cases (cited from other writers) which he grouped with them. Since then, many further accounts of sarcoidosis with nervous semeiology have been published, and extensive references to the literature of the subject are given in recent review articles adding other examples (Colover, 1948; Pennell, 1951; Jefferson, 1952; Aszkanazy, 1952; Meyer *et al.*, 1953).

The general picture that emerges is that no part of the nervous system is immune, but that the commonest sarcoid lesions are in the cranial and peripheral nerves. Optic neuritis or papillitis, external ocular palsies, pupillary abnormalities, trigeminal sensory loss, facial palsy, loss of taste, nerve-deafness, weakness or paralysis of the palate and pharynx, vocal cords or tongue may all occur, alone or in any combination, and are usually transient. There is no doubt that, of all these, paralysis of the seventh nerve is the most frequent, and is bilateral remarkably often, either more or less simultaneously or with but a short time interval between. In the limbs there may be motor and sensory signs, again transitory, with depression or abolition of tendon reflexes, the objective pattern sometimes suggesting peripheral nerve damage or at other times radicular involvement, or the two may be mixed. Root pains and segmental or patchy dysæsthesia may be present in the trunk.

All these manifestations of peripheral neuropathy, which may be localized or widespread, may accompany or succeed cranial nerve lesions, or can appear independently of them, and a sequential course of events with the evolution of new neurological features whilst others recede is not unusual.

Rather less often there is involvement of the central nervous system, which may take a wide variety of forms. There may be signs of cerebral hemisphere damage, presenting with general or focal fits, motor or sensory hemiplegia, homonymous field defect, speech disturbance, mental confusion or personality change. Cerebellar signs with nystagmus and ataxia may occur, or extrapyramidal syndromes of quasi-Parkinsonian or other types. The hypothalamic-pituitary area seems a particularly favoured site for sarcoid lesions. Sometimes headache and papillœdema are present, and neoplasm in the supratentorial compartment or posterior fossa is simulated. The brain-stem or spinal cord may be affected, in a manner to suggest degenerative disease or compression by tumour. On the whole sarcoid affliction of the central neuraxis, whether cranial or spinal, does not show the evanescence which marks its peripheral lesions, but tends to produce disorders which are either static or slowly progressive.

Lastly, signs and symptoms of meningeal sarcoid involvement may be met, taking the form either of subacute, chronic, or latent meningitis, or of solitary granuloma of the meninges. In either event it is rare for signs of accompanying nervous disorder to be absent. The cerebrospinal fluid protein content is increased, with positive globulin tests, and first or midzone Lange curve, and mild to moderate lymphocytic pleocytosis.

Material

The following cases of sarcoidosis affecting the nervous system exemplify the diversity of the clinical pictures which may be met. The first two had cranial nerve lesions alone, the third had cranial and central nervous lesions, the fourth, fifth, and seventh central lesions only, and the sixth a meningeal sarcoid granuloma.

Case 1.—R. C. (3920050328), male, age 23, a railwayman, admitted to the Queen Elizabeth Hospital, Birmingham, on November 28, 1951. Twelve days earlier he had woken to find the sight in his left eye blurred, as though by a pink fog. In the next few days there was further deterioration in the left eye, and the right became similarly affected. Two days before, the left side of his face felt stiff, and he discovered that he could not close the eye or eat properly.

Previous medical history.—In the last two years he has had four attacks of acute iritis, with intraocular hæmorrhage, each time recovering in a few weeks.

On examination.—V.A.R. 6/24. Right eye: perilimbic injection, large vitreous hæmorrhage obscuring fundus. V.A.L. 6/18. Left eye: similar appearances, but vitreous hæmorrhage less extensive. Slit lamp: keratic precipitates bilaterally.

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Complete left-sided lower motor neurone facial palsy, with loss of taste in left half of tongue.

Investigations.—Chest X-ray: hilar gland enlargement and pin-point opacities both lung fields. Full blood count: R.B.C. 5·68 m., Hb. 15·7 grammes per cent (114 per cent), C.I. 1·00, W.B.C. 6,500 normal differential. Serum albumin 4·0 grammes per cent, globulin 1·3 grammes per cent. Serum sodium 331 mg. per cent, potassium 18·4 mg. per cent, calcium 11·6 mg. per cent. Serum free cholesterol 56 mg. per cent, ester cholesterol 204 mg. per cent. Mantoux negative at 1/1,000 and 1/100. X-rays of hands and feet normal.

Course.—The diagnosis of sarcoidosis was made and treatment with cortisone, 50 mg. daily given for six weeks. There was satisfactory resorption of the vitreous hæmorrhages with recovery of visual acuity, and by the time of discharge from hospital on January 15, 1952, the left facial palsy had largely cleared up. However, less than a fortnight later, the patient developed a right facial palsy which became complete in the course of a morning, and next day the sight on the right dimmed again. He was readmitted to the Queen Elizabeth Hospital on January 30, 1952, and treated on this occasion with calciferol, 50,000 units daily for four weeks, treatment being checked with repeated examination of the urine for evidence of renal damage, frequent blood urea and serum calcium estimations, and straight X-rays of the renal tract. Once more recovery of the ocular and facial conditions was fairly rapid, and was complete when discharged on February 29, 1952.

The patient's progress in the last four years has been marked by many other episodes of retinal and vitreous bleeding, leading (during 1955) to right-sided retinal detachment, and further courses of treatment with calciferol, cortisone or ACTH have been ineffective in preventing relapse. There have been no further neurological developments, but complaints of tiredness, productive cough, and shortness of breath have appeared, and serial chest X-rays have shown persistent enlargement of the hilar shadows. There have been no skin lesions, or superficial lymphadenopathy.

Summary.—A man of 23 developed signs of bilateral iritis with intraocular hæmorrhage, shortly followed by acute facial palsy with ageusia. There was recovery from these complaints in a few weeks, but paralysis of the opposite side of the face occurred soon afterwards, again accompanied by intraocular bleeding. There was a previous history of ocular inflammation and hæmorrhage for two years before these events. The Mantoux reaction was negative, and radiography of the chest showed enlargement of the hilar lymph nodes. In the last four years there have been many repetitions of uveitis, and cough and breathlessness have gradually developed. Serial chest films have demonstrated persistence of the enlarged hilar shadows.

Case 2.—R. D. (3924010526), male, age 30, a clerk, admitted to the Queen Elizabeth Hospital, Birmingham, on June 29, 1956. Six weeks ago his eyes both became inflamed, and vision was slightly hazy, but there was no pain and he did not consult his doctor, as he thought he had simple conjunctivitis. This condition lasted about a month. Nine days ago, he woke with a slight headache. When he spoke to his wife he found that the left side of his face did not move properly, and he could not close his eye. From his account the paralysis was evidently total from the start. Six days later, the right side became completely paralysed also, but was slower in development, taking about thirty-six hours. No disturbance of taste noticed, but

his mouth has felt dry for a day or two. Otherwise he has been perfectly fit, and has been at work till now.

Previous medical history.—Four and a half years ago, he had a febrile illness with cough, sputum which was slightly bloodstained, and pain in the right side of the chest. His general practitioner diagnosed pneumonia, and treated him at home with sulphonamide. The cough and fever subsided in two weeks, but he remained short of breath, and was referred for chest X-ray at hospital. Signs of right basal collapse were found, with a small pleural effusion, from which a few c.c. were aspirated. The fluid was turbid, and contained white cells (74 per cent eosinophils). There were no organisms in a direct smear, and forty-eight-hour culture was negative. Culture for tubercle bacilli was also negative. In three months chest X-ray was clear again, and he was perfectly fit. No other past illnesses except the usual childhood ailments.

On examination.—Complete facial diplegia of lower motor neurone type. Pupils irregular, with posterior synechiæ and pigmented keratic precipitates bilaterally. Slight but definite bilateral parotid swelling. Spleen and liver not palpable, no superficial lymphadenopathy. No chest or cardiovascular signs. Afebrile.

Investigations.—Chest X-ray: enlarged hilar glands, segmental atelectasis right mid-zone, old calcified primary lesion left mid-zone. X-ray of hands: no bone lesions. Blood count: Hb. 14·5 grammes per cent (98 per cent), W.B.C. 8,100. Red and white cells normal in stained films. E.S.R. 11 mm./hour (Wintrobe). Serum albumin 4·8 grammes per cent, globulin 1·9 grammes per cent. Serum sodium 130 m.eq./l., potassium 4·6 m.eq./l., chloride ion 102 m.eq./l., calcium 12·0 mg. per cent. Serum alkaline phosphatase 9·0 units per cent (Jenner and Kay). Blood W.R. and Kahn negative. Mantoux reaction positive at 1/1,000. Conjunctival biopsy: gross chronic conjunctivitis with heavy infiltration of round cells, polymorphs, histiocytes and fibroblasts. No typical sarcoid follicular arrangement seen.

Course.—Sarcoidosis was diagnosed and oral cortisone prescribed, starting with 100 mg. daily and gradually reducing to 25 mg., treatment being continued for six weeks. Eye drops (atropine ½ per cent, and cortisone 1 per cent) were also given. The parotid swelling subsided in a short time, and on discharge from hospital on July 15, 1956, the right facial palsy had partially recovered, though no sign of left sided recovery was visible. His progress was subsequently followed as an out-patient, and by the end of September 1956, there was full recovery of the right face, and beginning improvement on the left. He had returned to work, and felt well.

Summary.—A 30-year-old man developed bilateral iridocyclitis followed a few weeks later by left-sided and then right-sided facial palsy together with mild parotid swelling. Three years earlier there had been a febrile illness with pain in the chest and productive cough, with radiological signs of a small pleural effusion and basal lung collapse. X-rays now showed enlarged hilar lymph nodes and segmental atelectasis in the right mid-zone. The Mantoux reaction was positive at 1/1000. The parotid swelling rapidly recovered, the right facial palsy more slowly, with improvement of the left side subsequently. Conjunctival biopsy was inconclusive.

Case 3.—W. H. (4645210925), male, age 29, a corporation employee, admitted to the General Hospital, Birmingham, on July 28, 1955. Three and a half months ago he felt generally unwell. After a few days his right eye became inflamed and painful, and the sight deteriorated. Five days later the left eye was similarly affected.

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The diagnosis of acute iritis was made at hospital, and treatment with cortisone eye drops given. The uveitis recovered slowly in about eight weeks, but meanwhile (two months ago) he began to have headaches of gradually increasing severity. Three weeks ago unsteadiness of gait appeared, which now prevents him from standing or walking without support. Four days ago right sided facial palsy developed.

Previous medical history.—Since the age of 5 he has had recurrent swellings of lymph nodes in the neck, and elsewhere, which have never broken down, for which the diagnosis of tuberculous adenitis has often been suggested. From the age of 20 onwards, there have also been several episodes of inflammation of the eyes.

On examination.—Bilateral mild papillœdema. Slight nystagmus looking to either side. Impairment of touch and pin-prick in right trigeminal distribution, including right half of tongue. Corneal reflex diminished on right. Complete right facial palsy of lower motor neurone type. No cerebellar signs in limbs when tested lying in bed, but severe cerebellar ataxia evident in trying to stand or walk. Palpable lymph nodes left side of neck and both groins.

Investigations.—Chest X-ray: hilar glands enormously enlarged on both sides. Skull X-rays: normal, including Stenver's views. X-ray of hands: normal. Blood count: R.B.C. 5·02 m., Hb. 14·8 grammes per cent (100 per cent), C.I. 1·00, W.B.C. 4,600, normal differential. E.S.R. 5 mm./hour (Westergren). Serum albumin 3·5 grammes per cent, globulin 3·1 grammes per cent. Serum calcium 9·2 mg. per cent, phosphorus 3·2 mg. per cent. Blood W.R. and Kahn negative. C.S.F. protein 40 mg. per cent, 1 lymph./c.mm. C.S.F. W.R. negative. Mantoux negative at 1/1,000, weak positive at 1/100.

Course.—It was considered that the patient was suffering from sarcoidosis with lesions affecting the fifth and seventh cranial nerves, and damaging the cerebellar vermis to produce loss of balance, the latter lesion evidently being of sufficient magnitude to produce the rise in intracranial pressure indicated by slight papillœdema and headache.

He was treated with calciferol, 50,000 units daily for a month, during which careful check was kept on the serum calcium and phosphorus levels, and on renal function. At the end of this time, his balance was nearly perfectly recovered, papillœdema had gone, and there was no nystagmus or trigeminal sensory defect, though but little improvement in the facial palsy had taken place. An attack of severe conjunctivitis came on during his stay in hospital, which was treated with chloramphenicol ointment and atropine drops. He was discharged from hospital on September 16, 1955.

Progress was observed subsequently as an out-patient. By October 6, 1955, the right facial palsy was about 50 per cent recovered, but he still felt very easily tired, and was inclined to be breathless. In January 1956 he reported considerable improvement in general well-being, and there was now little sign of facial weakness. Chest X-ray showed slight but definite diminution of size of hilar nodes. He returned to work in April 1956, and has been essentially well since although mild conjunctivitis has appeared several times, and lymph nodes in the neck have been swollen and tender at times. A further chest radiograph in August 1956 demonstrated no change.

Summary.—A man of 29 developed bilateral acute iritis, with malaise. A few weeks later headache came on, followed by increasing unsteadiness in walking, and finally by right facial palsy. Examination disclosed mild papillœdema, slight nystagmus, impaired trigeminal sensibility on the right, right lower motor neurone paralysis of the face, and severe cerebellar ataxia of stance and gait, pointing to cerebellar vermis damage.

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There was some superficial lymphadenopathy, and a strong past history (covering nearly twenty-five years) of recurrent lymph-node swelling in the neck and elsewhere, with attacks of ocular inflammation for about nine years. Radiography of the chest demonstrated greatly enlarged lymph node shadows at the hila. The Mantoux reaction was negative at 1/1,000, but weakly positive at 1/100. There was increase in the serum globulin content, with an albumin : globulin ratio approaching unity. Neurological symptoms all cleared up eventually, but shortness of breath and excessive tiredness remained for several months, and there has since been persistent radiological evidence of enlarged hilar lymph nodes.

Case 4.—G. G. (1933310812), male, age 43, a rubber worker, admitted to the Queen Elizabeth Hospital, Birmingham, on September 2, 1955. Four and a half years ago, he began to have focal epileptic attacks, starting with paroxysmal tingling around the left side of the mouth, and leading to clonic twitching of the left side of the face, with paralysis of speech. The episodes would last perhaps five minutes, leaving transient post-ictal motor dysphasia. At first their incidence was not high, but now they happen at least once a week, and during the last six months have sometimes tended to affect the left arm with twitching as well. He has become embarrassed over their frequent occurrence at work which has led to his being sent home often, with consequent loss of wages.

Previous medical history.—He has had recurrent attacks of rheumatic pain in the joints of variable severity since the age of 16, but otherwise cannot recall any illnesses.

On examination.—Slight upper motor neurone weakness of left side of face, but no other signs in the central nervous system. Left ankle definitely swollen, and movements restricted. Lipoma in lumbar region.

Investigations.—Skull and chest X-rays: normal. X-ray of left ankle: normal. Blood count: R.B.C. 5·54 m., Hb. 15·7 grammes per cent (114 per cent), C.I. 1·03, W.B.C. 6·400, normal differential. Blood W.R. and Kahn negative. C.S.F. pressure normal, protein 43 mg. per cent, cells 2 lymphs./c.mm. C.S.F. W.R. negative. Lumbar pneumoencephalography: no displacement or distortion of the ventricular system. EEG: occasional low voltage waves at 5½—6 c/s in the right parietal area with many small sharp deflections. No signs of phase reversal.

Course.—It was thought that the patient's focal fits stemmed from a localized area of cortical atrophy of unknown (but presumably) benign ætiology. Since he was insistent that something must be done to stop his attacks, craniotomy was undertaken with the idea of excising the causal epileptogenic focus. A right parietal osteoplastic flap was turned, and the dura found adherent to the cortex over the inferior end of the motor cortex just above the Sylvian fissure. Electrocorticography indicated a focal high voltage slow wave discharge not over the area of cortical adhesions, but in the lower part of the post-central gyrus, which corresponded well with the sensory onset of the fits. This portion of the gyrus, which felt hard, was excised, and subsequent electrocorticography showed practically no abnormality. The wound was closed in layers in the usual manner. It was thought that the diseased cortex and meningeal adhesions were probably due to old inflammation. Postoperatively there was no increase in facial weakness, and no objective motor or sensory signs in left limbs, but subjectively the arm and face felt "a bit strange."

Histological examination of the portion of cortex and white matter removed showed a chronic granulomatous reaction, with a distinct follicular pattern (fig. 1,

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Plate LXV). There were pale endothelial cells in the centre of the follicles, which were surrounded by a zone of lymphocytes and plasma cells. No giant cells were present, and no caseation or necrosis was observed. No organisms were detected in Ziehl-Neelsen or Gram stains. In view of the nature of the tissue reaction, the diagnosis of sarcoid was suggested. In consequence of this, the patient was questioned more closely about his past history. It transpired that he had had an attack of uveitis when he was 23, with pain, photophobia, conjunctival injection, and difficulty in seeing. He was away from work on account of it for six months, part of which he had spent in hospital. It also turned out that three or four weeks before his first fit he had what was called influenza, the symptoms being malaise, headache and fever. With it there was a return of ocular inflammation similar to, but less severe than, the previous attack, as well as recrudescence of polyarthritis.

Careful examination now demonstrated that old posterior synechiæ were visible in the left eye, when dilated with homatropine, and a small area of left iris atrophy of post-inflammatory type. Small soft lymph nodes were palpable in the right axilla, and at the left elbow. The Mantoux reaction was tested, and found negative at 1/1,000 and 1/100. Serum albumin 4·1 grammes per cent, globulin 1·4 grammes per cent. Reinspection of the chest X-ray, previously accepted as normal, suggested that there was in fact enlargement of the left hilar shadow. X-rays of the hands were normal. The further points in history and clinical signs thus brought out established that the patient was suffering from sarcoidosis with diffuse systematized lesions, and not simply from a solitary sarcoid granuloma of the brain. He was discharged from hospital on October 1, 1955.

Seen six months later he reported he had only had one seizure when he had woken in the night to find his left arm shaking, but there was no affection of the face. A year after operation he was well, though he had had two or three further attacks, all restricted to the arm. EEG (October 1956) now showed a well-defined focal spike discharge in the right parietal region, the waves being either single or in clusters. There was also some patchy theta activity at 4–7 c/s throughout the right hemisphere.

Summary.—A 43-year-old male patient had a four and a half year history of focal epileptic fits, gradually becoming more and more frequent, and handicapping him in his work. Left upper motor neurone facial weakness was the only physical sign noted. Local excision of the area of cortex responsible stopped the seizures. The tissue removed contained sarcoid lesions. More detailed questioning then established that there was a past history of 2 attacks of uveitis, one twenty years earlier, and the other (which was accompanied by headache, malaise and fever) in the weeks immediately preceding the appearance of the first fit. There was also a history of recurrent polyarthritis for many years. The Mantoux was negative at 1/100, and radiography of the chest indicated mild unilateral hilar enlargement. There was evidence of old iritis and slight superficial lymphadenopathy.

Case 5.—P. H. (400164), male, age 46, a shopkeeper, admitted to the Queen Elizabeth Hospital, Birmingham, on January 23, 1956, as an emergency. The history had to be obtained from the patient's wife, who stated that in the last two years he had gained 4 stone in weight, had had marked polydipsia, drinking many pints of water each day, with polyuria, and had completely lost libido. Three weeks ago he began to complain of sudden very violent, but transient, occipital headaches,

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and seemed abnormally tired so that he fell asleep in his chair in the evenings which was quite unusual for him. In the last week episodes of coarse tremor of the limbs had been apparent, and he had slept much of the time. Yesterday he had become even more drowsy and had been confused, with slow and almost incomprehensible speech. In the last twenty-four hours he had also had several bouts of shivering and profuse sweating.

Previous medical history.—No details discovered.

Examination.—Drowsy and very slow mentally, only partially co-operative. Obese. Bodily hair sparse. Skin cold, temperature 86° F. Pulse 40/min. B.P. 75/50. No papillœdema. Visual fields and acuity cannot be tested. Pupils small, poor light reaction. Tendon reflexes all sluggish. Abdominals absent. Plantars weakly extensor.

Investigations.—Urine (catheter specimen): S.G. 1,004, no sugar or acetonuria, albumin +++, no cells, casts or organisms. X-rays of skull and chest: no radiological abnormalities. EEG: bilateral slow wave dysrhythmia, no signs of focus. Ventriculography: dilatation of lateral ventricles, third ventricle incompletely filled. Ventricular C.S.F.: protein 74 mg. per cent, Pandy and Nonne-Apelt +, Lange curve 1122110000. Less than 1 white cell/c.mm. Blood count: Hb. 17·0 grammes per cent (115 per cent), W.B.C. 8,500, normal differential. Red cells normal in stained films, and platelets numerous. Serum sodium 147 m.eq./l., serum potassium 4·8 m.eq./l., serum chloride ion 111 m.eq./l., serum urea 48 mg. per cent. Blood W.R. and Kahn negative.

Course.—The clinical history clearly indicated a progressive hypothalamic disturbance, which was thought to be due to a glioma, and myodil ventriculography was proposed to try to outline the third ventricle which had only been partially visualized in the air studies. However, the patient died about ninety-six hours after admission, having gradually lapsed into deep coma, which was unaffected by hypertonic magnesium sulphate enemata. A striking feature throughout was his poikilothermia, body temperature only being kept up artificially with an electric blanket, and dropping rapidly as soon as it was removed or switched off.

At autopsy, the brain showed slight convolutional flattening, and mild tentorial grooving of the medial surface of the temporal lobes. The optic tracts and chiasma were enveloped in a brownish gelatinous mass which had the appearance of a glioma growing downwards from the region of the floor of the third ventricle, thus seeming to confirm the diagnosis made in life. The pituitary was macroscopically normal. The brain was preserved for section after fixation. In the chest, there were small bilateral pleural effusions, the lungs were congested, and their cut surfaces showed patchy consolidation and œdema in the lower lobes. The bronchi contained purulent material, and there was mucosal congestion. The hilar lymph nodes were much enlarged, pinkish-grey and fleshy, having the appearance of reactive hyperplasia. The heart was normal. There was post-mortem autolysis of the œsophageal mucous membrane, but the stomach and intestines were normal. Liver congested, some fatty change. Spleen normal. Kidneys congested. Pancreas normal. In the suprarenals there was diffuse ante-mortem hæmorrhage, destroying the medulla. The bladder, prostate and thyroid were normal.

Study of histological sections of tissues removed at post-mortem gave unexpected evidence. The "tumour" in the floor of the third ventricle, which extended upwards towards the thalamus on either side and also invaded the optic chiasma and tracts, proved to be composed of conglomerations of typical sarcoid follicles, in spite of its macroscopic resemblance to a glioma (fig. 2). The follicles contained epithelioid cells, with occasional giant cells; caseation was absent but there were some foci of

fibrinoid necrosis. The diagnosis of systematized sarcoidosis was clinched by the presence of similar sarcoid follicles in profusion in the hilar lymph nodes, and (less numerously) in the lungs and liver. There was also hæmorrhagic bronchopneumonia, and the suprarenal hæmorrhages were due to ante-mortem thrombosis of both suprarenal veins.

Summary.—A 46-year-old man was admitted to hospital as an emergency. It appeared that for two years he had steadily been gaining weight (4 stone), and had had polyuria and polydipsia with loss of libido. For three weeks there had been violent headache and abnormal fatigue. For one week he had been sleeping most of the time and had shown coarse tremor at times. For twenty-four hours he had been confused, and constantly drowsy; there had also been bouts of shivering and sweating. No details of past history were available. On examination he was rousable, but very slow mentally. His body was obese, with sparse pubic and axillary hair, and cold skin, his temperature being only 89° F. and his pulse rate very slow with a low blood pressure. The diagnosis of tumour invading the hypothalamus, probably intrinsic, was made. Coma gradually deepened, and death occurred on the fifth day. At autopsy the macroscopic appearance of the brain seemed to confirm the diagnosis of hypothalamic glioma, but histology later established the diagnosis of sarcoidosis, affecting hypothalamus, optic tracts, pulmonary lymph nodes, lungs and liver.

Case 6.—J. R. (361406), male, age 27, a builder's plasterer, admitted to the Queen Elizabeth Hospital, Birmingham, on June 9, 1955. For a year, he had been having brief frontal headaches, recurring three or four times every day and sometimes accompanied by vomiting. He had also been having frequent episodes of vertigo, in which objects seemed to move from left to right. The latter were daily events and during them he had to clutch hold of something for support; unlike the headaches they had gradually become both more common and more severe. He had also noticed slight unsteadiness of gait for the last twelve months, and for six months had had misty vision, with flashes of light before both eyes brought on by stooping. Lately effort had induced transient pins and needles in all four limbs.

Previous medical history.—Has been troubled by psoriasis since the age of 5. No other illnesses noted.

On examination.—Widespread psoriasis, especially of scalp. Bilateral papillœdema. Peripheral constriction of visual fields demonstrated with rough confrontation tests, and confirmed by perimetry, but visual acuity 6/6 and J2 bilaterally. Left pupil irregular, both react normally. Fine horizontal nystagmus on lateral fixation to either side, rotatory when looking upwards. No dysarthria or evidence of cerebellar deficit in control of limbs when tested lying in bed, but definite cerebellar ataxia apparent in stance and gait. Knee and ankle jerks somewhat exaggerated. On two occasions during examination, the patient had curious attacks, each time immediately after sitting up from the supine position. In each he fell back against the pillow, from a sudden accession of general weakness, lasting about three minutes. There was no headache or disturbance of consciousness. They were succeeded by bilateral deafness lasting twenty minutes, so that he was unable to hear the examiner's voice, or a tuning fork on the mastoids, although he could feel its vibration.

Questioned later, he said he had had a few previous similar attacks, and that there was purring tinnitus during them but no other sensation.

Investigations.—Skull X-rays: normal. Ventriculography: pressure of ventricular C.S.F. raised, chemistry and cytology normal. Air replacement showed enlarged lateral ventricles. Myodil (4 ml.) instilled into lateral ventricle. Third ventricle and aqueduct dilated, no displacement. Fourth ventricle also large, no escape of contrast medium from roof.

Course.—The combination of nystagmus, trunk ataxia, and papillœdema with headaches, vomiting, and visual disturbance all pointed clearly to a posterior fossa expanding lesion, which was thought likely to be an intrinsic tumour of the cerebellar vermis. The episodes of weakness and deafness brought on by change of posture suggested upset of posterior fossa hæmodynamics, and were interpreted as meaning that medullary pressure coning was already established. After ventriculography, posterior fossa craniotomy was undertaken straight away. During bone removal, the patient stopped breathing, and the lateral ventricle had to be tapped to reduce intracranial pressure. A wide exposure was quickly made including taking away the posterior margin of the foramen magnum and the arch of the atlas. When the dura was incised, marked downward displacement of the cerebellar tonsils was found. The 4th ventricle could not be seen on separation of the tonsils, but on needling resistance was felt in the mid-line at a depth of 1 cm. Vertical incision in the lower medial portion of the right cerebellar hemisphere exposed a firm indefinite mass, part of which was removed. A greatly dilated 4th ventricle was then entered, the mass seeming to be attached both to its roof and partly also to the back of the medulla in its floor. Most of it was removed, and C.S.F. circulation restored by opening the ventricle widely. The dura was left open, and the wound closed in layers. The macroscopic appearances at operation suggested that the mass was an ependymoma, but the histology of frozen sections showed a granuloma, possibly tuberculous in nature. Intraventricular streptomycin (0·2 gramme) was therefore injected before the patient left the operating table.

Post-operatively, in view of the provisional biopsy report, there was much anxiety that tuberculous meningitis might ensue, and vigorous anti-tuberculous treatment was instituted with intramuscular streptomycin (1 gramme daily), and alternating intraventricular or intrathecal streptomycin (0·1 gramme) and isonicotinic acid hydrazide (25 mg.) daily. For nearly a fortnight, the patient remained gravely ill, but no signs of meningitis declared themselves, and then he slowly began to pick up.

In the meantime more detailed histological study indicated that the portions of tissue removed showed atrophic cerebellum with thickening of the overlying meninges from infiltration by granulation tissue containing giant cell systems, and foci of epithelioid cells (fig. 3). There was no caseation, and no acid-fast bacilli were found. The cerebellar tissue was not directly involved. The question of sarcoidosis was raised, and further investigations were undertaken with this in mind. The Mantoux reaction proved negative at 1/1,000, 1/100 and 1/10, and chest X-ray disclosed definite enlargement of both hilar lymph node shadows with a few small opacities in both lung fields. Re-examination of the eyes under homatropine showed posterior synechiæ bilaterally, more severe on left than right, and the patient now recalled, when asked directly, that he had had some kind of ocular inflammation two or three years ago, but could give no exact details.

It was concluded that the diagnosis of sarcoidosis was established and anti-tuberculous treatment was stopped five weeks after operation. Further affirmation was given not long after by negative results of animal inoculation and culture on media selective for tubercle bacilli of several specimens of C.S.F. On August 15, 1955, the patient was transferred from the Queen Elizabeth Hospital back to a hospital

elsewhere, whence he had originally been accepted. At this stage he was just beginning to walk. His further progress is unknown.

Summary.—A man of 27 gave a twelve-month story of headache, vertigo, and slight unsteadiness of gait, and for six months his sight had been failing. Recently he had had episodes of general weakness and deafness brought on by sudden movement of the head. He had also found that physical effort induced transient paræsthesiæ in all four limbs. Examination showed bilateral choking of the optic discs, fine nystagmus, and cerebellar ataxia of gait and stance. A mid-line cerebellar (vermis) glioma was suspected. At operation a mass was found filling the fourth ventricle, arising from its roof, which was largely removed. Frozen sections showed the tissue to be granulomatous, possibly tuberculous, and intensive anti-tuberculous treatment was started to prevent the development of tuberculous meningitis. After an initially turbulent post-operative phase, the patient gradually began to recover, and meanwhile more detailed histological examination of tissue removed at operation established that the granuloma was of sarcoid type. The patient now recalled, on direct questioning, that he had had uveitis two or three years earlier, and under homatropine, posterior synechial adhesions were found bilaterally. Chest X-ray disclosed bilateral hilar gland enlargement, and the Mantoux was negative down to 1/10. Animal inoculation and selective culture of material from the granuloma were negative for tubercle bacilli. These points provided confirmatory evidence of sarcoidosis, and anti-tuberculous treatment was stopped.

Case 7.—A. P. (320605), aged 66, a housewife, admitted to the Queen Elizabeth Hospital, Birmingham, on October 16, 1953. For the last five years, she has had focal epileptic seizures, starting with jerking of the left arm and leg, and leading to unconsciousness with generalized convulsion. At first they were extremely frequent, happening several times a day, but with phenobarbitone their incidence has dropped to about one a week. During the last sixteen months there has been slowly progressive weakness of the left arm and leg, with shooting pains of considerable severity radiating from the shoulder to the fingers of the left hand. For three months she has had attacks of sudden vomiting, not related to meals, and without indigestion. Headache has been absent throughout.

Previous medical history.—No serious illnesses described.

On examination.—An obese woman, mentally clear but not at all co-operative. Severe weakness of upper motor neurone type in left limbs, arm worse than leg, with spasticity and exaggerated tendon reflexes. Left plantar extensor. Gross defect of postural sense in left hand and foot, with some diminution of touch and pin-prick, and vibration sense, in the left limbs. B.P. 190/120.

Investigations.—Skull and chest X-rays normal. Blood W.R. and Kahn negative. Ventriculography normal. Ventricular C.S.F.: protein 17 mg. per cent, no cells, W.R. negative. Right carotid angiography: normal intracranial vascular pattern.

Course.—Because of the history of fits, focal on the left side, with left-sided neurological signs in arm and leg, it was naturally assumed that there was a lesion in the right cerebral hemisphere, probably a tumour in view of the history of vomiting

which suggested raised intracranial pressure. However, neither ventriculography nor angiography demonstrated any intracranial abnormality. It was then noted that the patient had a left-sided Horner's syndrome, with slight ptosis and pupillary narrowing, which suggested that (in spite of the fits) the causal lesion might be in the cervical cord. Myelography was done and demonstrated subtotal block at C.6, apparently due to intrinsic tumour extending up to C.3–4 level. The lumbar C.S.F. contained a raised protein (128 mg. per cent, with positive globulin tests) and a moderate pleocytosis (66 lymphocytes).

Exploratory cervical laminectomy disclosed an intrinsic tumour in the left side of the cord dorsally. A small portion was taken for histological examination, and the wound closed in the usual manner. The biopsy report indicated that the tissue was not neoplastic, but granulomatous, containing a heavy infiltration of round cells (lymphocytes), associated epithelioid cells with follicular arrangement and occasional giant cells. No caseation was present, and acid-fast bacilli were not found, nor did special stains demonstrate any parasitic organisms. Post-operatively, the patient was completely relieved of pain in her left arm, but there was no recovery of power. A week after operation, she suddenly became unconscious, and had a generalized convulsion. Shortly afterwards breathing ceased, and in spite of artificial respiration, oxygen and intramuscular nikethamide, quickly died.

At autopsy the significant findings were small whitish foci in the cut surfaces of the lungs, becoming confluent in places, and enlarged hilar lymph nodes. The brain showed no macroscopic abnormality, and the cord no special features except a small vertical incision dorsally in the mid-cervical region from the recent operation together with slight enlargement at this level. Cord and brain were then fixed in formalin for later study. Histological examination demonstrated numerous sarcoid foci in the pulmonary lymph nodes, with epithelioid and giant cells, and surrounding lymphocytes with occasional eosinophils. In many follicles peripheral collagenous fibrosis was present. There were numerous similar sarcoid lesions in the lungs, and a few tiny follicles in the liver. Extensive sarcoid lesions were present in the pia-arachnoid and cord itself in the cervical region some of which showed intracytoplasmic inclusions (Schaumann bodies) in giant cells (fig. 4). Microscopy of sections of medulla, pons, hypothalamus and cortex showed no changes apart from well-marked congestion and a few ring hæmorrhages. Culture and animal inoculation tests on tissues taken at autopsy were negative for tubercle bacilli.

Summary.—A 66-year-old woman complained of fits with focal onset in the left limbs of five years' duration, and for about a year and a half had had slowly progressive weakness of these limbs, with severe pains in the left arm. For three months she had been vomiting without obvious cause. There was upper motor neurone paralysis of the left side, not including the face, with left-sided sensory loss chiefly affecting postural sense. Because of the fits and vomiting she was suspected of having a cerebral tumour, but ventriculography and angiography were normal. It was then observed that the patient had a left Horner's syndrome, and myelography demonstrated a tumour in the mid-cervical cord. This was confirmed at laminectomy, the macroscopic appearance suggesting a glioma, but biopsy proved it to be a granuloma. Death came unexpectedly a week after operation, from cessation of respiration after a fit. At autopsy typical sarcoid lesions were present in the cervical cord, pulmonary lymph nodes, lungs and liver. The brain was normal.

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Discussion

The diagnosis of sarcoidosis of the nervous system poses no great difficulty if symptoms and signs of sarcoid affection of other organs are there to give the key, like swollen salivary glands or superficial lymph nodes, cutaneous eruptions, uveitis, or chest symptoms with radiographic signs. The latter may take the form of fanlike striation radiating from the hila, miliary or larger nodular shadows in the lung fields, diffuse opacities, and enlargement of hilar lymph nodes with consequent increase of the root shadows. Such pointers are frequently present simultaneously with cranial and peripheral nerve manifestations or are readily discernible in the past history, but with lesions of the central nervous system they are generally either absent or so insignificant that they are easily overlooked. In such circumstances, the neurological symptoms themselves are then only an anatomical signature of the locus of disease, which give no intimation of pathology beyond what may be inferred from their course in time. So correct diagnosis becomes a formidable matter, and as a rule is only made after histological examination of biopsy material taken at craniotomy or laminectomy, or comes as a surprise at post-mortem.

In the first 3 cases, evidence of extraneural sarcoidosis was sufficiently plain to make recognition simple, and little comment on them is called for. In Case 1, the main presenting feature was recurrent intraocular hæmorrhage, conforming to the pattern of bleeding secondary to retinal vasculitis, first described by Henry Eales (1880, 1882). This is now generally accepted as a condition which may be met in a number of diseases, amongst them sarcoidosis (Ballantyne and Michaelson, 1937; Benedict and Wagener, 1940; O'Malley, 1944). In Case 2, the simultaneous bilaterality of the facial palsies was enough to raise the possibility of sarcoid immediately, because acute facial diplegia from any other cause is so rare. With regard to the Mantoux reaction in this case and in Case 3, it can be said that only about three-quarters of patients with sarcoidosis give the classical negative response, and a positive test cannot therefore be taken to countermand the diagnosis. The remaining 4 cases were much more teasing. In 2 (Cases 4 and 6), it was possible to establish historical and clinical evidence of systematized sarcoid affections, once the histology of the neurological lesions had been revealed; in Case 4, they included recurrent polyarthritis which is known as an occasional sarcoid sign (Longcope and Freiman, 1952; James, 1956). Case 6 resembles other examples of sarcoid granuloma of the posterior fossa which have been published (Erickson *et al.*, 1942; Colover, 1948; Pennell, 1951). In Case 5, full anamnesis was impossible because of the patient's comatose state, but widespread lesions were demonstrated after post-mortem. As already mentioned the hypothalamus and pituitary are amongst the commonest sites of intracerebral attack by

sarcoid, and there are quite a number of well-documented cases on record (Tillgren, 1935; Wahlgren, 1937; Hannesson, 1941; Kraus, 1942; Gjersøe and Kjerulf-Jensen, 1950; Pennell, 1951; Aszkanazy, 1952; and others). Indeed, sarcoid involvement of this region is interesting, because lesions here seem to differ somewhat in their behaviour from other cerebral lesions. First, they may appear in frank association with acute episodes of sarcoidosis of other tissues, and secondly, the symptoms produced may be only transitory, both of which are otherwise uncommon characteristics. So, for instance, diabetes insipidus lasting a few weeks or months may occur. Such a case was amongst Heerfordt's (1909) originals, and a good many more have been reported not only in the uveoparotid syndrome but also in company with cutaneous and pulmonary symptomatology.

In Case 7, no history of previous illness to suggest sarcoidosis clinically was obtained, although again widespread sarcoid granulomas were present at autopsy. Why the patient had focal fits was not established, however, for there was neither macroscopic nor microscopic damage in the cerebral hemispheres; it is curious that they should have been lateralized to the limbs which were later damaged by sarcoid granuloma in the cervical cord. The reason for the patient's death in apnœa after a fit also remains unexplained.

The present series of cases throw no light on the troublesome question of the ætiology of sarcoidosis. The hypothesis that it is a modified form of tuberculosis has been popular for a good many years, although the causal rôle of Koch's bacillus has never been proven. It rests on two main premises, each dubious. The first is the histological resemblance of sarcoid follicles to tubercles, but most morbid anatomists would agree that this is no warrant of identity of pathogenesis. Indeed it is now generally recognized that the sarcoid follicle itself is not a specific microscopic entity, for it has been reported in a great many conditions, including various bacterial infections (amongst them leprosy, syphilis and brucellosis), parasitic and protozoal diseases (for example ascariasis and leishmaniasis), mycoses, metabolic disorders such as Whipple's disease, as a result of exposure to chemical agents (notably beryllium), from drugs, and even in neoplasia. The second cornerstone is the observation that a number of patients with sarcoidosis die ultimately with signs of frank tuberculosis, which (it is suggested) means that there is a change at a late stage in host response to tubercle bacilli primordially responsible for the condition so that classical, instead of atypical, lesions now appear. But this fact can equally well be interpreted as an index of lowered resistance to intercurrent infection. In this context Hodgkin's disease provides a parallel on several points. Like sarcoidosis it is a malady in which the reticulo-endothelial system is the target tissue, the majority of its sufferers are negative tuberculin reactors (Dubin,

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1947; Hoyle *et al.*, 1954), and terminal tuberculosis is a recognized phenomenon probably in about the same proportion of cases as in sarcoidosis, though reliable statistics are hard to come by in either. Dubin (1947) has found evidence of poverty of cutaneous and general immunological reactions in Hodgkin's disease, which he believes means inefficiency of antibody production, and so accounts for heightened susceptibility to infection of all kinds, including tubercle. The same argument may well bear extension to sarcoidosis, particularly as it has shown that in it too there is depression of cutaneous immunological reactivity to antigens other than tuberculin (Friou, 1952; Sones and Israel, 1954).

Another hypothesis is that sarcoidosis is an infection of unknown ætiology, possibly viral, and the claim of Löfgren and Lundbäck (1950) to have isolated a virus of influenza-mumps-Newcastle disease group from a number of typical cases is interesting in this regard, though so far it has not been substantiated by others. Lastly, there is the relatively recent notion that sarcoidosis may not be an ætiologically pure condition, but is a syndrome of essentially hyperergic type which may have multiple causes. In view of the lack of specificity, just referred to above, of the sarcoid lesion as a histological phenomenon, it is by no means inconceivable that sarcoidosis is a diffuse fixed tissue reaction whose clinical standardization, in point of history, course and organs affected, is also imposed by the relatively limited repertory of responses which the human body can make to a large variety of pathogenic influences. On this assumption the isolated sarcoid lesion and the clinical entity of sarcoidosis are both representatives of a single reactive process, the one remaining local and the other being systematized, the difference depending on the individual and the provocative noxa concerned. If this concept of sarcoidosis is correct, it would put the condition into the same general group of systematized tissue antigen-antibody disorders as polyarteritis nodosa, disseminated lupus erythematosus, paramyloidosis and other collagenoses. It has received support from several quarters (Merrill and Oaks, 1931; Lewis *et al.*, 1936; Teilum, 1948; Rosenthal, 1949; van Ordstrand, 1951; Churg and Strauss, 1951; Jaques, 1952; Meyer *et al.*, 1953; Jackson and Kass, 1953; Kass *et al.*, 1954), and seems to have much to recommend it.

Summary

The manifestations of sarcoidosis as it affects the nervous system, peripheral and central, are described, and 7 cases are reported.

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REFERENCES

ASZKANAZY, C. L. (1952) *J. Neuropath.*, **11,** 392.
BALLANTYNE, A. J., and MICHAELSON, I. C. (1937) *Brit. J. Ophthal.*, **21,** 22.
BENEDICT, W. L., and WAGENER, H. P. (1940) *Amer. J. med. Sci.*, **199,** 296.
BOECK, C. (1907) Cited by Salvesen, H. A.
BRUINS SLOT, W. J. (1936) *Ned. Tijdschr. Geneesk.*, **80,** 2859.
——, GOEDBLOED, J., and GOSLINGS, J. (1938) *Acta med. scand.*, **94,** 74.
CHURG, J., and STRAUSS, L. (1951) *Amer. J. Path.*, **27,** 277.
COLOVER, J. (1948) *Brain*, **71,** 451.
DUBIN, I. N. (1947) *Ann. intern. Med.*, **27,** 898.
EALES, H. (1880) *Bgham. med. Rev.*, **9,** 262.
EALES, H. (1882) *Ophthal. Rev.*, **1,** 41.
ERICKSON, T. C., ODOM, G., and STERN, K. (1942) *Arch. Neurol. Psychiat., Chicago*, **48,** 613.
FRIOU, G. J. (1952) *Yale J. Biol. Med.*, **24,** 533.
GJERSØE, A., and KJERULF-JENSEN, K. (1950) *J. clin. Endocrin.*, **10,** 1602
HANNESSON, H. (1941) *Brit. J. Tuberc.*, **35,** 88.
HEERFORDT, C. F. (1909) *v. Graefes Arch. Ophthal.*, **70,** 254.
HOYLE, C., DAWSON, J., and MATHER, G. (1954) *Lancet*, **2,** 164.
JACKSON, A., and KASS, I. (1953) *Ann. intern. Med.*, **38,** 288.
JAMES, D. G. (1956) *Brit. med. J.*, **2,** 900.
JAQUES, W. E. (1952) *Arch. Path.*, **53,** 550.
JEFFERSON, M. (1952) *Brit. med. J.*, **2,** 916.
KASS, I., JACKSON, A., and SLAVIN, M. (1954) *J. Allergy*, **25,** 453.
KRAUS, E. J. (1942) *J. Lab. clin. Med.*, **28,** 140.
LEWIS, G. E., RAINES, R., and STEWART, D. S. (1936) *Lancet*, **2,** 1204.
LÖFGREN, S., and LUNDBÄCK, H. (1950) *Acta med. scand.*, **138,** 71.
LONGCOPE, W. T., and FREIMAN, D. G. (1952) *Medicine, Baltimore*, **31,** 1.
LONGCOPE, W. T., and PIERSON, J. W. (1937) *Bull. Johns Hopk. Hosp.*, **60,** 223.
MAZZA, G. (1908) Cited by Salvesen, H. A.
MERRILL, H. G., and OAKS, L. W. (1931) *Amer. J. Ophthal.*, **14,** 15.
MEYER, J. S., FOLEY, J. M., and CAMPAGNA-PINTO, D. (1953) *Arch. Neurol. Psychiat., Chicago*, **69,** 587.
O'MALLEY, C. L. C. (1944) *Trans. ophthal. Soc. U.K.*, **64,** 261.
PAUTRIER, L. M. (1937) *Bull. Soc. méd. Hôp. Paris*, **53,** 1608.
PENNELL, W. H. (1951) *Arch. Neurol. Psychiat., Chicago*, **66,** 728.
ROSENTHAL, S. R. (1949) *Amer. Rev. Tuberc.*, **60,** 236.
SALVESEN, H. A. (1935) *Acta med. scand.*, **86,** 127.
SONES, M., and ISRAEL, H. L. (1954) *Ann. intern. Med.*, **40,** 260.
TEILUM, G. (1948) *Amer. J. Path.*, **24,** 389.
TILLGREN, J. (1935) *Brit. J. Derm.*, **47,** 223.
URBAN, O. (1910) Cited by Salvesen, H. A.
VAN ORDSTRAND, H. S. (1951) *Ann. intern. Med.*, **35,** 1203.
WAHLGREN, F. (1937) *Nord. med. Tidskr.*, **13,** 965.
WINKLER, M. (1905) Cited by Salvesen, H. A.

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LEGENDS FOR PLATE

PLATE LXV

FIG. 1.—Typical sarcoid follicles in portion of parietal cortex removed surgically (Case 4). The epithelioid cells show some tendency to arrangement in whorls. Hæmatoxylin and eosin. × 100.

FIG. 2.—Follicle in sarcoid granuloma of hypothalamus (Case 5). Luxol fast blue. × 125.

FIG. 3.—Granuloma of 4th ventricle infiltrating meninges (Case 6). Epithelioid cells, some giant cells, and round cells. No caseation. Atrophic cerebellum. Hæmatoxylin and eosin. × 50.

FIG. 4.—Intracytoplasmic inclusions in giant cells in sarcoid granuloma of cervical cord (Case 7). Hæmatoxylin and eosin. ×230.

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PLATE LXV

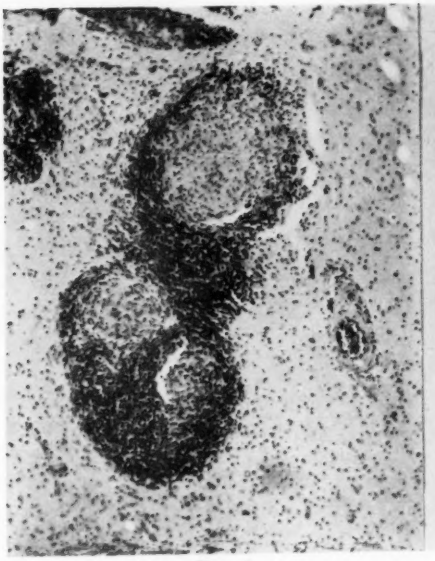

FIG. 1.

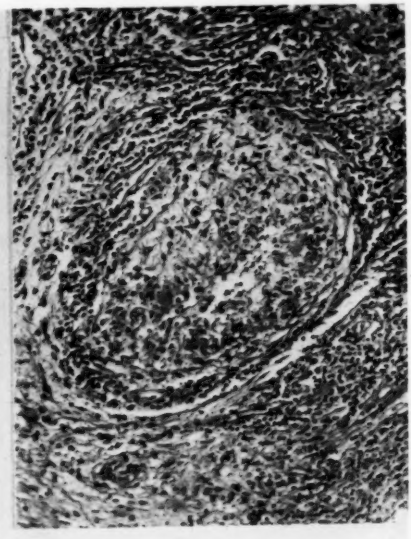

FIG. 2.

FIG. 3.

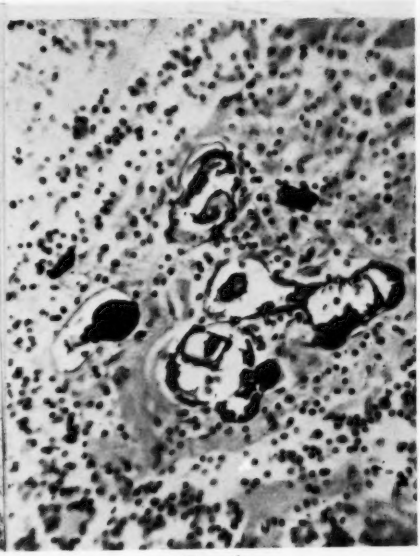

FIG. 4.

To illustrate article by Michael Jefferson.

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SERUM ALDOLASE AND THE DIAGNOSIS OF MYOPATHY

BY

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INTRODUCTION

ALDOLASE is an enzyme which catalyses the reversible splitting of fructose–1:6-diphosphate into two triose esters, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. The enzyme is present in many tissues of the body, but its greatest concentration is found in striated muscle where in the rabbit it comprises 4 per cent of the water-soluble proteins (Herbert, Gordon, Subrahmanyan and Green, 1940). Under normal conditions feeble aldolase activity, that is less than one-hundredth the activity of an equivalent weight of muscle, can be detected in the serum. It is presumed that this serum aldolase activity is due to the escape of intracellular enzyme into the circulation by diffusion through the cell membrane or by the degeneration of effete cells.

Interest in the clinical value of serum aldolase assay was aroused by Warburg and Christian (1943) who reported increased aldolase activity in the serum of rats infected with transmissible neoplasms, although this increased activity was not apparent until the tumour had exceeded 2–3 per cent of the total body weight (this would correspond to a tumour weighing 1·4 to 2·1 kg. in a 70 kg. man). Investigating 104 patients with malignant diseases, Sibley and Lehninger (1949*b*) showed that the serum aldolase was elevated above the normal range in 20 per cent of cases. It was concluded that the mean serum aldolase level in the patients with cancer differed significantly from the normal mean, but that in an individual case the test was of no diagnostic value. In the same report, elevation of the serum aldolase was described in two patients with muscular dystrophy.

Sibley and Fleisher (1954) determined the serum aldolase level in 880 patients with various diseases. The values were within normal limits in 115 patients with functional psychiatric complaints, orthopædic conditions and benign tumours. Increased aldolase activity was found in 2 out of 5 patients with primary muscle disease. In addition, high levels were frequently found in hæmolytic anæmia, delirium tremens, acute hepatitis

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and acute hæmorrhagic pancreatitis. High levels were occasionally found in pneumonia, diabetes mellitus, ulcerative colitis, myxœdema, and tissue infarction. It was concluded that in many of those diseases in which increased serum aldolase activity had been found, the common factor was rapid tissue destruction with the release of the intracellular enzyme into the circulation.

Jacob and Neuhaus (1954), using a modification of Sibley and Lehninger's method, estimated the serum aldolase activity in 10 patients with Erb's muscular dystrophy. The serum aldolase was elevated above the normal range in all patients. The two lowest values were found in the only females in the series. In one patient with dystrophia myotonica and in 13 patients with muscular atrophy of neuronal origin, the serum aldolase was normal.

Schapira, Dreyfus and Schapira (1953), using the technique devised by Sibley and Lehninger (1949*a*) and modified by Dounce, Barnett and Beyer (1950), also studied the serum aldolase in muscular dystrophy. The normal mean in ten healthy children, aged 6 to 15 years, was nearly double that in 7 healthy adults. The results in 29 children and 11 adults with non-myotonic muscular dystrophy were presented. In all of the adults and in all but three children the normal maximum was exceeded, reaching levels ten times the mean normal value in two adults and ten children. No clinical details were given, but the authors found no correlation between the rate of progress of the disease, or the severity of muscular wasting, and the serum aldolase activity. The serum aldolase was also elevated in three adults with dystrophia myotonica. By contrast with the high levels in primary muscle disease, the serum aldolase was normal or only slightly elevated in 18 cases of acute poliomyelitis examined within twenty weeks of the onset of paralysis, and in eight patients with chronic neurogenic muscular atrophy.

It is clear that abnormal serum aldolase levels are not peculiar to the myopathies and that they may be found in many diseases in which there is rapid cellular destruction. Within the group of muscle diseases, however, there is evidence to support the diagnostic value of the method in distinguishing primary muscle disease from neurogenic muscular atrophy. Hitherto no attempt has been made to relate the serum aldolase to the various types of myopathy. This investigation was therefore designed to correlate the serum aldolase with the clinical picture and to assess its diagnostic value in patients with muscular weakness and wasting. In addition, animal experiments were performed to throw light on the origin of the excess serum aldolase in muscle disease.

The most convenient method of aldolase assay is that described by Sibley and Lehninger (1949*a*). In this method the triose phosphates formed by the splitting of fructose–1:6–diphosphate are trapped by hydrazine so that the reverse reaction cannot take place and the triose

cannot be metabolized by other enzymes present in the serum. The phosphate moiety is removed from the triose esters by exposure to sodium hydroxide at room temperature, and the triose osazone is then formed by incubation with 2:4–dinitrophenylhydrazine. The osazone mixture is made alkaline and the resulting colour is proportional, over a wide range, to the amount of osazone present. To obtain reliable results it is essential to ensure precise control of temperature, and accurate timing of the duration of each reaction.

Aldolase Assay

Reagents:

0·1M Trishydroxymethylaminomethane (Tris)–HCl buffer, pH 8·6.
0·56M Hydrazine—HCl buffer, pH 8·6.
10 per cent (w/v) trichloroacetic acid.
0·75 N NaOH.
0·1 per cent (w/v) 2:4–dinitrophenylhydrazine (DNPH) in 2N HCl; filtered before use.

Substrate solution, 0·025M sodium fructose–1:6–diphosphate. For the substrate, commercial calcium fructose diphosphate (Light and Co.) was purified by conversion to the barium salt. Aliquots of this, suspended in water, were then converted to the sodium salt by ion-exchange with the sodium form of the sulphonated polystyrene resin Z 225 (Permutit). The solution thus obtained was brought to correct volume and stored at −15° C.

Method.—1·0 ml. Tris solution, 0·25 ml. hydrazine solution and sufficient water to make the final volume 2·25 ml. were mixed, in glass-stoppered tubes, with a suitable volume, 1·0 ml. or less, of serum or of plasma from heparinized blood, and brought to 38·0° C. 0·25 ml. substrate solution was then added, and the mixture was incubated at 38·0° C. for 30 min. before precipitation with 2·0 ml. 10 per cent trichloroacetic acid. For blank tubes, the substrate was added after precipitation. Supernatant (1·0 ml.), obtained by centrifuging for 10 min., was transferred to glass-stoppered tubes containing 1·0 ml. 0·75N NaOH and standing in a bath at 20° C. After exactly 10 min., allowed for hydrolysis of the triose phosphate, 1 ml. DNPH was added and osazone formation allowed to proceed at 38° C. for 30 min. (Beck, 1955). The tubes were immediately transferred to the bath at 20° C. and left for 5 min. Then 7·0 ml. 0·75 N NaOH were added. Exactly 10 min. later the optical density was read against water with a Spekker absorptiometer, using 1 cm. cells and filter 605. In order that our results should be directly comparable with those of other workers, the readings have been interpreted in terms of aldolase units (A.U.) which represent (Sibley and Lehninger, 1949*a*) the number of μl. substrate split in one hour by 1 ml. serum under the conditions described (22·4 μl. of substrate $\equiv$ 1 μM.).

To determine the quantitative relationship between the optical density measured and the corresponding value in aldolase units, we carried out a series of analyses in which both the optical density and the amount of alkali-labile phosphate formed, i.e. triose phosphate, were measured on the same incubation mixture. Since these experiments involved the estimation of

phosphate, dialysed serum was employed together with substrate specially purified through the strychnine salt (Sable, 1952). The incubation was conducted at pH 7·2 to obviate interference from serum phosphatase. Varied quantities of serum were used to give data at different levels of activity. For determination of alkali-labile phosphate, 2 ml. were taken from each protein-free supernatant of the incubation mixture and treated with an equal volume of 0·75 N NaOH for 10 min. at 20° C, after which the solution was acidified with 0·8 ml. 60 per cent perchloric acid. Control 2 ml. aliquots were also taken from each supernatant, and acidified before addition of the alkali. The final quantities of inorganic phosphate were determined by the method of Ernster, Zetterström and Lindberg (1950). The control samples gave values for pre-existing inorganic phosphate, so that by difference the amount of triose phosphate formed during the incubation could be calculated.

The variation of aldolase activity with change in hydrogen ion concentration is of a low order. Our results showed that at pH 8·6 the activity of serum was greater by about 10 per cent than at pH 7·2.

Results

Normal Values

The range of serum aldolase levels in 25 healthy adults was found to be 3·1 to 6·6 units (Mean 4·86, S.D. ±0·86). Sibley and Lehninger (1949*b*) studied 68 adults and established a normal range of 3·5 to 8·0 units (Mean 4·9).

Serum was also obtained from eleven children under 14 years who were convalescent from an infection or who had been admitted for orthopædic conditions. The range was 3·5 to 11·7 units (Mean 7·58, S.D. ±2·06). This is admittedly not a normal series, but the high values found in children as compared with those in adults were also noticed by Schapira *et al.* (1953), who found that the mean serum aldolase in children was twice that in adults.

In neither group was there any significant difference between the mean level in males and in females, nor was there any correlation between the serum aldolase and the age of the patients within each group.

Serum Aldolase in Diseases of Muscle

64 patients were examined. The diagnosis was usually made on clinical grounds although electromyography and muscle biopsy provided confirmatory evidence in some cases. Classification of the muscular dystrophies followed the criteria suggested by Walton and Nattrass (1954), but the term "pseudohypertrophic muscular dystrophy" has been retained in favour of "childhood muscular dystrophy—Duchenne type."

Children.—In each of the 9 patients with *pseudohypertrophic muscular dystrophy* there was a striking elevation of the serum aldolase which was never less than twice the upper limit of the normal range (Table I). There was no correlation between the aldolase activity and the duration, severity, or rate of progress of the disease, or with the amount of pseudohypertrophy evident on clinical examination.

TABLE I.—SERUM ALDOLASE ACTIVITY IN CHILDREN WITH MUSCLE DISEASE.
(Expressed as μl. substrate split/ml./hour)
Normal values from 11 children: 3·5–11·7. (Mean 7·58, S.D. ±2·06)

	Case	*Age (years)*	*Sex*	*Activity*	
Pseudohypertrophic muscular dystrophy	NF	5	M	145·4	
	DP	8	M	90·2	
	KE	8	F	68·5	Mean = 67·3
	JM	8	M	60·7	S.D. = ±35·3
	DR	8	M	51·5	t = 6·3
	GM	9	M	77·5	p = 0·001
	DO	9	M	48·5	
	GC	9	M	37·8	
	JF	10	M	25·8	
Myopathic form of amyotonia congenita	JS	11	F	9·0	
Amytonia congenita	AH	8 wks.	M	8·7	
	KH	21 ms.	F	10·1	
	NG	$2\frac{1}{2}$	M	4·0	Mean = 6·06
	RH	4	F	6·0	S.D. = ±2·55
	SC	5	F	3·8	t = 1·48
	MK	8	M	3·5	p = 0·1
	HK	8	M	6·4	

By contrast, normal serum aldolase activity was invariably found in six children with *amyotonia congenita* and in one patient with the *myopathic form of amyotonia congenita* whose case-history was similar to those described by Turner (1940).

Adults.—Four adults with *pseudohypertrophic muscular dystrophy* also showed an elevated serum aldolase (Table II).

In the *facio-scapulo-humeral dystrophy* group a raised serum aldolase was found in 2 out of the 5 patients but the elevation was slight. In the *limb-girdle dystrophy* group the serum aldolase was elevated in 4 out of 5 patients.

As in the children there was no correlation between the serum aldolase level and the severity or progress of the disease.

In 1 patient with *myotonia congenita* the serum aldolase was raised. Of 11 patients with *dystrophia myotonica* there was slight elevation in 4, but the mean of the group was not significantly different from the normals ($p=0{\cdot}02$).

In 6 patients with *polymyositis*, high serum aldolase levels were found in 2 who presented the chronic form of this disease. In these 2 patients the serum aldolase remained constant during treatment with cortisone or corticotropin. During the period of observation there was no apparent response to therapy and their clinical condition continued to deteriorate.

TABLE II.—SERUM ALDOLASE ACTIVITIES IN ADULTS WITH PRIMARY MUSCLE DISEASE

(Expressed as μl. substrate split/ml./hour)

Normal values from 25 adults: 3·1–6·6. (Mean 4·86, S.D. ± 0·86)

	Case	*Age (Years)*	*Sex*	*Activity*	
Pseudohypertrophic muscular dystrophy	DM	17	M	30·7	Mean = 22·8
	JJ	18	M	22·6	S.D. = ± 7·4
	EG	23	M	24·8	t = 12·8
	PC	48	M	13·0	p = 0·001
Facio-scapulo-humeral muscular dystrophy	JA	22	M	6·0	Mean = 6·54
	EJ	22	M	6·8	S.D. = ± 1·58
	LP	43	M	6·4	t = 3·45
	FF	47	M	8·9	p = 0·01
	FM	56	F	4·6	
Limb-girdle muscular dystrophy	BB	35	F	30·7	Mean = 14·5
	SL	39	F	7·2	S.D. = ± 11·42
	JL	47	M	22·5	t = 4·47
	RS	48	F	6·9	p = 0·001
	EO	58	F	5·2	
Myotonia congenita	DL	28	M	10·4	
Dystrophia myotonica	JM	23	F	4·3	
	RD	29	F	5·6	
	DH	31	M	4·6	
	LB	36	M	8·1	Mean = 5·87
	MS	41	F	7·3	S.D. = ± 1·65
	PS	42	M	7·1	t = 2·62
	OF	45	F	5·4	p = 0·02
	WG	49	M	4·6	
	MW	54	F	7·0	
	FH	54	M	3·8	
	JR	61	M	6·7	
Acute polymyositis	FF	54	M	3·1	
	HP	57	M	4·6	
					Date
Chronic polymyositis	GA	36	M	21·6	3.1.56
				19·1	14.2.56
				22·0	27.3.56
				22·6	8.5.56
				20·1	20.6.56
Chronic polymyositis	HW	58	F	10·3	19.3.56
				9·4	16.4.56
				10·8	11.5.56
				8·9	12.6.56
Recovering chronic polymyositis	CT	67	F	4·1	
	BB	15	F	5·5	

The serum aldolase was normal in 8 out of 9 patients with *chronic neurogenic muscular atrophy* (Table III) in whom the rapidity and extent of muscular wasting was similar to that found in the patients with muscular dystrophy.

TABLE III.—SERUM ALDOLASE ACTIVITY IN NEUROGENIC MUSCLE DISEASE
(Expressed as μl. substrate split/ml./hour)

	Case	*Diagnosis*	*Age (years)*	*Sex*	*Activity*	
Chronic neurogenic muscular atrophy	RK	Acute polyneuritis	49	F	2·9	
	TW	Acute polyneuritis	35	M	4·3	
	GA	Syringomyelia	36	M	5·8	
	EG	Motor neurone disease	65	F	5·7	Mean = 4·68 S.D. = ± 1·15
	ME	Atypical peroneal muscular atrophy	18	F	4·9	t = 0·32 p = 0·1
	NF	Peroneal muscular atrophy	32	F	2·7	
	FS	Peroneal muscular atrophy	23	M	3·8	
	EH	Peroneal muscular atrophy	49	M	6·7	
	AH	Cervical spondylosis	62	M	4·8	

	Case	*Age*	*Sex*	*Day of Disease*	*Extent of Paralysis*	*Activity*
Acute paralytic poliomyelitis	DL	44	F	6	All limbs and intercostals	5·6
	DL	44	F	12	All limbs and intercostals	6·5
	AJ	12	M	6	Palatal and pharyngeal	5·1
	BF	30	F	7	Right arm	4·8
	FI	27	F	5	Both legs	12·1
	FI	27	F	12	Both legs	7·8
	FI	27	F	19	Both legs	6·5
	JH	33	M	42	Left leg	6·0
	SB	37	F	42	Both legs and right arm	6·9

In 6 patients with *acute paralytic anterior poliomyelitis* (Table III) the serum aldolase was elevated in 2. In Case F.I. the level was 12·1 units on the fifth day of the disease but fell towards the normal range in the next two weeks. The cause of this transient rise in the serum aldolase is unknown.

Plasma Aldolase Levels in Vitamin E-deficient Rabbits

Additional information about the source of the serum aldolase was obtained by studying rabbits which had been fed on a diet deficient in fats and the fat-soluble vitamin E, but containing adequate amounts of the other vitamins, protein and carbohydrate. These animals were

kindly supplied by Dr. J. Cavanagh and Dr. I. Macdonald. After three months on this diet the rabbits became ill and emaciated. The skeletal musculature was wasted and weak, but not tender. In one rabbit miscroscopy of the tissues after death showed degeneration in the posterior nerve root ganglia and the posterior columns of the spinal cord, but there was no abnormality of the lower motor neurones. The muscles were affected by focal necrosis and a reactive infiltration with macrophages (Macdonald, personal communication). The liver was slightly fibrotic but showed no evidence of necrosis.

These animals were comparable to patients with myopathy in that the muscles, and not the motor neurones, were primarily affected. The histological picture more closely resembled human myositis than dystrophy.

In view of the difficulty in obtaining unhæmolysed rabbit's serum, blood from the marginal vein of the ear was collected into a tube containing heparin. After mixing, the contents of the tube were immediately centrifuged and the supernatant plasma removed.

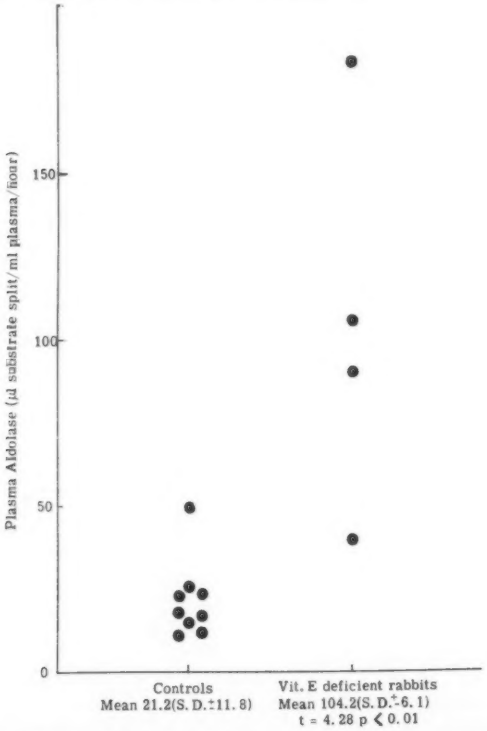

FIG. 1.—Plasma aldolase levels in vitamin E-deficient rabbits.

Control levels were obtained from 9 young adult healthy rabbits and the results are shown in fig. 1. The normal range is much wider than in man.

The plasma aldolase was measured in 4 adult rabbits which had been on the vitamin E-deficient diet for two and a half months; the results are shown in fig. 1. A marked elevation of the plasma aldolase was found in these rabbits, and the difference between the two groups is statistically significant.

It is probable that the source of the increased plasma aldolase in these rabbits is the affected muscle, but it is also possible that the degenerating sensory nerves may have contributed significantly to the increased serum aldolase. Moreover the occasional findings of a raised serum aldolase in patients with acute paralytic poliomyelitis might be explained by loss of enzyme from degenerating neurones. The opportunity to investigate this point is provided by the selective effect of tri-*ortho*-cresyl phosphate (TOCP) on the nervous system.

Plasma Aldolase of Chickens poisoned with Tri-ortho-*cresyl Phosphate*

1 ml. TOCP/kg. body-weight when given to chickens produces, within about 10–14 days, weakness and ataxia, accompanied by changes in the axons and myelin sheaths in the spinal cord and peripheral nerves (Cavanagh, 1954). With this dosage spontaneous recovery occurs without microscopic change in the muscle supplied by the affected motor nerves.

1 ml. TOCP/kg. body-weight was administered by stomach tube to four chickens by Professor R. H. S. Thompson. Between two and three weeks later the poisoned birds were obviously affected. They crouched on their heels with wings incompletely retracted. On being persuaded to walk they quickly became tired and were less squawky than the control birds. They were killed by decapitation and the blood was collected in heparin tubes. Four control birds were killed at the same time.

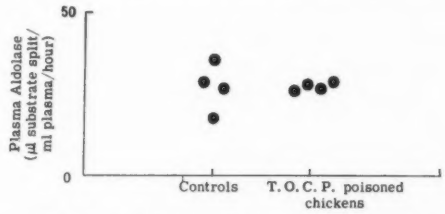

FIG. 2.—Plasma aldolase levels in chickens poisoned with tri-*ortho*-cresyl phosphate.

The results show no detectable difference in the plasma aldolase activity of the two groups (fig. 2). There is therefore no evidence that degeneration of the peripheral nerves causes a raised serum aldolase.

Discussion

These results both substantiate and amplify previous reports. The high levels of the serum aldolase in pseudohypertrophic muscular dystrophy in this series are comparable with the levels in childhood muscular dystrophy found by Schapira *et al.* (1953). They, too, found no correlation between the serum aldolase and the degree of muscular involvement. They also reported high levels in all cases of adult muscular dystrophy, a higher incidence than in this series where the normal range was exceeded in only 10 out of 14 patients with non-myotonic muscular dystrophy.

The invariable elevation of the serum aldolase reported by Jacob and Neuhaus (1954) in 10 cases of Erb's muscular dystrophy, which we are classifying as limb-girdle dystrophy, is not confirmed for one normal level was found in 5 of our patients. There is no evidence, moreover, that the level in females with this disease is lower than in males as is suggested by their results. The finding, reported by Sibley and Fleisher (1954), that 2 out of 5 cases of muscular dystrophy or myositis had an elevated serum aldolase is not inconsistent with the results presented here.

The slightly elevated serum aldolase which Schapira *et al.* (1953) found in dystrophia myotonica is confirmed.

There is, therefore, good evidence that the serum aldolase tends to be elevated in muscular dystrophy, especially in the pseudohypertrophic form of the disease. In neurogenic muscular atrophy the serum aldolase is usually normal.

Our finding that the plasma aldolase activity is raised in rabbits with nutritional myopathy, but not in chickens poisoned with TOCP is in accord with the clinical results.

Little is known about the distribution of aldolase in the body fluids. No aldolase activity was found in three specimens of cerebrospinal fluid. Activity was present in the pleural fluids of patients with post-pneumonic effusion, carcinoma of the bronchus and congestive cardiac failure, and in the ascitic fluid of a patient with portal hypertension. No aldolase activity was detected in urine obtained from 3 normal individuals and from 4 patients with pseudohypertrophic muscular dystrophy.

On theoretical grounds the excess serum aldolase in myopathy might be expected to arise from the diseased muscle because in normal rats this tissue contains nearly five times as much aldolase as any other (Sibley and Lehninger, 1949*b*). Experimental support of this hypothesis is given by Dreyfus, Schapira and Schapira (1954) who have studied the aldolase activity of normal and dystrophic muscle obtained by biopsy. They point out the error in relating enzymic activity to unit weight of the muscle because of the increased amounts of fat and fibrous tissue that are found in diseased muscle. They therefore refer the aldolase activity to the non-collagen nitrogen (a term applied to the nitrogen content of that portion of the muscle that is soluble in dilute alkali), which is the

best index of the amount of muscle tissue in the specimen. Their results show that the aldolase content of dystrophic muscle is about one-third that of the normal figure.

Furthermore, there is evidence to suggest that other enzymes are lost from the diseased muscle. Dreyfus, Schapira, Schapira and Demos (1956) showed that the activities of phosphorylase and phosphoglucomutase were low in dystrophic muscle, whereas the activity of these enzymes in the serum of the same patients was above normal. On the other hand they found that the activities of cytochrome oxidase, succinic dehydrogenase, aconitase and fumarase did not differ from the normal range in the muscles and serum of patients with muscular dystrophy. In unpublished observations we have found that the transaminase activity of the serum was increased in 7 out of 14 patients with myopathy. It is concluded that the excess serum aldolase in primary muscle disease merely represents a more generalized loss of water-soluble protein from the affected muscle fibres.

It is becoming increasingly apparent that many familial diseases are due to the absence or derangement of a particular enzyme system, and that this effect if closely related to the hereditary nature of the disease. It is clear, however, that the increased activity in the serum of aldolase and other enzymes does not directly represent a primary biochemical abnormality in muscular dystrophy. The inconstant and variable diffusion into the blood stream of unrelated intracellular enzymes does not fulfil the role of a genetically determined solitary enzymic defect.

Nevertheless the sera of possible carriers of the recessive gene were examined to find out whether there was any asymptomatic disturbance of muscle biochemistry. Four mothers of children with pseudohypertrophic muscular dystrophy were examined and the results are shown in Table IV.

TABLE IV.—SERUM ALDOLASE ACTIVITY OF THE MOTHERS OF CHILDREN WITH PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY
(Expressed as μl. substrate split/ml./hour)

Mother of Case	*Activity*
NF	5·5
KE	5·2
GC	4·6
JF	4·7

The results were all within normal limits, but only in Case N. F. was there any family history of the disease. In the remaining 3 patients the disease may have been due to a mutation, and the carrier state of the mothers cannot be assumed.

CLINICAL APPLICATION OF SERUM ALDOLASE ASSAYS

In practice the diagnosis of muscular dystrophy can usually be made at the bedside. It is in the early stages, or in unusual forms, of the disease that confusion may arise, and then laboratory aid may be sought.

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Accurate diagnosis is of practical importance in advising parents that other children may be affected or may carry the recessive gene.

A biopsy of one of the affected muscles is the most satisfactory investigation but under certain circumstances this cannot be done or further evidence is required. Electromyography is diagnostic in fully-developed myopathy but in early cases its evidence may be equivocal. The 24-hour output of urinary creatine and creatinine may be disturbed in many wasting diseases. The creatine tolerance test is more specific in suggesting the presence of myopathy (Cumings, 1953), but this test requires careful supervision of diet and urine collection. Ribosuria is an inconstant finding in the myopathies, and also occurs in other diseases of muscle.

The value of the serum aldolase level in distinguishing myopathy from neuronal disease has to be considered in the light of the findings of Sibley and Fleisher (1954) who showed that the serum aldolase is raised in a variety of disorders. It is important to make sure that the patient has no other disease, particularly hepatitis, tissue infarction, delirium tremens or hæmolytic anæmia, in which high levels are found. If these diseases can be excluded from the differential diagnosis, a raised serum aldolase is strongly suggestive of primary muscle disease. A normal serum aldolase on the other hand, is of less diagnostic value because normal levels may be found in severe muscular dystrophy with the exception of the pseudohypertrophic form. The test does not help to differentiate between polymyositis and muscular dystrophy.

Serum aldolase assay would seem to be of particular value in the diagnosis of pseudohypertrophic muscular dystrophy because of the invariable and marked elevation of the activity of this enzyme in the serum in this disease. An early or atypical case which presents a diagnostic problem usually occurs in childhood when it is advantageous to be able to obtain confirmatory evidence without resorting to muscle biopsy. If only a small quantity of blood is available for examination, a positive result can be obtained from a little over 0·2 ml. serum (0·1 ml. for the assay and 0·1 ml. for the blank).

The following case-history emphasizes that the aldolase level does not appear to be related to the severity of the disease and that it may be greatly elevated in the early stages, just when the clinical diagnosis may be difficult to make.

Case W. F., aged 5 years, attended hospital with his brother who had pseudohypertrophic muscular dystrophy. W. F. developed normally until the age of 2 when he had started to complain of pains in his legs on walking. On examination he was a thin child who had normal muscle power on formal testing, and all tendon-jerks were present. However his calves were rather prominent and he had a little difficulty in getting up from the floor. The diagnosis was in doubt clinically. His serum aldolase was 145·5 units and 127·9 units on two separate occasions.

The value of the test in excluding pseudohypertrophic muscular dystrophy is illustrated by the following 2 case histories.

A male clerk (A. B.) of 23 years, who had no relevant family history complained of vague intermittent aches in the bellies of his biceps and gastrocnemii for the previous two years. He was of spare build and no abnormality was found on clinical examination except for prominence of the first dorsal interossei, infraspinati, quadriceps and gastrocnemii. Muscle power was normal and all tendon-jerks were present. An atypical form of pseudohypertrophic muscle dystrophy was suspected. The serum aldolase was 4·2 units and a muscle biopsy revealed a normal histological picture. The diagnosis was, therefore, rejected.

The patient B. B. was a girl of 15 years who had an inoperable retroperitoneal ganglioneuroma which had not increased in size in the previous seven years. There was no relevant family history. At the age of six years she had started to walk on tip-toe. In the next year she was found to have pseudohypertrophy of the gastrocnemii and absent ankle-jerks. The deltoids, too, were rubbery in consistency. Two years later her gait was still waddling and she had to climb up her legs when rising from the floor. Since the age of nine years she had improved steadily. At the time of examination she walked heavily and had some aching in her calves on walking fast. She was obese and had genu valgum and pes cavus. There was no pseudohypertrophy nor contractures. Only the glutei were weak. All tendon-jerks were present. In retrospect this patient resembled those described by Nattrass (1954), and polymyositis was the most likely cause of her symptoms, but pseudohypertrophic muscle dystrophy had been diagnosed at the age of 7. The serum aldolase was 5·5 units.

The serum aldolase may also be of value in forecasting the onset of pseudohypertrophic muscular dystrophy before there is evident weakness in the male children of a possible carrier. So far the opportunity to do this has not arisen. There is no evidence that the serum aldolase is elevated in carriers of the disease.

It may be concluded that, as a convenient and simple procedure serum aldolase assay can serve as a useful investigation in confirming the diagnosis of myopathy, particularly when pseudohypertrophic muscular dystrophy is suspected.

Summary

(1) 64 patients with muscle disease were examined and the serum aldolase levels have been correlated with the clinical findings.

(2) In 13 patients with pseudohypertrophic muscular dystrophy gross elevation of the serum aldolase was invariably found. A raised level was frequently found in other types of muscular dystrophy and in polymyositis.

(3) Normal levels were found in 9 patients with chronic neurogenic

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muscular atrophy and in 6 children with amyotonia congenita. Of 6 patients with acute paralytic poliomyelitis the serum aldolase was slightly elevated in 2.

(4) The serum aldolase was normal in 4 mothers of patients with pseudohypertrophic muscular dystrophy.

(5) No aldolase activity has been detected in urine or cerebrospinal fluid.

(6) Plasma aldolase activity was elevated in rabbits with nutritional myopathy. By contrast the plasma aldolase levels were found to be normal in chickens exhibiting neuronopathy resulting from poisoning with tri-*ortho*-cresyl phosphate.

(7) The significance of these findings is discussed, and it is concluded that the increased serum aldolase in primary muscle disease is only one example of a generalized loss of enzymes from degenerating or necrotic muscle tissue.

(8) The clinical application of the test is discussed and it is concluded that it has its greatest value in the diagnosis of pseudohypertrophic muscular dystrophy.

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References

Beck, W. S. (1955) *J. biol. Chem.*, **212,** 847.
Cavanagh, J. B. (1954) *J. Neurol. Neurosurg. Psychiat.*, **17,** 163.
Cumings, J. N. (1953) *Brain*, **76,** 299.
Dounce, A. L., Barnett, S. R., and Beyer, G. T. (1950) *J. biol. Chem.*, **185,** 769.
Dreyfus, J. C., Schapira, G., and Schapira, F. (1954) *J. clin. Invest.*, **33,** 794.
——, ——, —— and Demos, J. (1956) *Clin. chim. acta, Amst.*, **1,** 434.
Ernster, L., Zetterström, R., and Lindberg, O. (1950) *Acta. chem. scand.*, **4,** 492.
Herbert, D., Gordon, H., Subrahmanyan, V., and Green, D. E. (1940) *Biochem. J.*, **34,** 1108.
Jacob, W., and Neuhaus, J. (1954) *Klin. Wschr.*, **32,** 923.
Nattrass, F. J. (1954) *Brain*, **77,** 549.
Sable, H. Z. (1952) *In* Ball's Biochemical Preparations, London. Vol. II, p. 52.
Schapira, G., Dreyfus, J. C., and Schapira, F. (1953) *Sem. Hôp. Paris*, **29,** 1917.
Sibley, J. A., and Fleisher, G. A. (1954) *Proc. Mayo. Clin.*, **29,** 591.
——, and Lehninger, A. L. (1949a) *J. biol. Chem.*, **177,** 859.
——, —— (1949b) *J. nat. Cancer. Inst.*, **9,** 303.
Turner, J. W. A. (1940) *Brain*, **63,** 163.
Warburg, O., and Christian, W. (1943) *Biochem. Z.*, **314,** 399.
Walton, J. N., and Nattrass, F. J. (1954) *Brain*, **77,** 169.

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THE CERVICAL SPINE

AN ANATOMICO-PATHOLOGICAL STUDY OF 70 SPECIMENS (USING A SPECIAL TECHNIQUE) WITH PARTICULAR REFERENCE TO THE PROBLEM OF CERVICAL SPONDYLOSIS

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DURING the past decade published accounts of radiological changes in the cervical spine have clearly shown that they are very common and are usually symptomless. Various associated cervical root and cord syndromes have been described and a number of pathological examinations have been reported. But any discussion of the topic of cervical spondylosis soon discloses that ideas vary considerably concerning the nature and sequence of the alterations in the spine, nerve roots and spinal cord. It is not always clear whether certain changes are those of normal ageing or the result of disease. Even the normal anatomy of the part is disputed. Thus, for example, the existence or otherwise of the "Luschka joints," and the slope of the emerging nerves are subjects about which very different statements are made. Lastly, there is the question of the nature of the pathological process implied by the term "cervical spondylosis." To some writers it is synonymous with "cervical osteoarthritis"; to others it is quite distinct from that disease.

This investigation was undertaken because it seemed to us that post-mortem studies of the cervical spine would help to provide an essential background of knowledge to this subject. In the past three years we have removed and studied 70 specimens obtained at routine autopsies in the Department of Pathology. Age and occupation are given in Table I. There were 56 males and 14 females. Sixty-four of the patients were over the age of 40.

The specimens have been prepared and sectioned by the Gough-Wentworth technique for thin sections of entire organs mounted on paper (1948). This method provided sections 400 to 600 microns in thickness in which normal structure and the alterations occurring with age could be inspected and recorded (fig. 1, Plate LXVI). The nutrition of the avascular intervertebral discs is by a process of diffusion from the marrow of the bodies of adjacent vertebræ through the cartilaginous end-plates. A study

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TABLE I.—AGE AND OCCUPATION OF 70 PATIENTS FROM WHOM CERVICAL SPINES WERE REMOVED AT AUTOPSY

Occupation	..	Sedentary	9		
		Manual	54		
		Not known	7		
Age 0– 9 years	..	4	50–59 years	..	23
10–19 years	..	1	60–69 years	..	19
20–29 years	..	1	70–79 years	..	10
30–39 years	..	0	80–89 years	..	3
40–49 years	..	9			

of thin serial sections of vertebræ and discs at different ages should help in our understanding of the relationships which must exist between these structures during life. "Disc degeneration" may be only one aspect of a process which actually begins within the vertebral bodies or in the cartilage plates and not primarily within the disc itself.

PROCEDURE

The 70 specimens examined were first X-rayed and then either (*a*) dissected, or (*b*) cut into thin serial sections. Some specimens were partially dissected and then used for thin sections so that the gross appearance could be correlated with that given by the sections. In addition small blocks for histology were cut from various parts of each specimen.

(*a*) *Removal of the cervical spine.*—The viscera and brain are removed in the routine manner. When only the cervical spine and spinal cord are required the cadaver is placed in the supine position with a block under the neck. A chisel incision is made which circles the foramen magnum from the inner side of the skull and passes posteriorly through the squamous occipital bone. The incision should first be marked out lightly and the deep incision then carried forward through the petrous temporal and basi-occipital bones. In this way cracking the squamous occipital bone is avoided.

When removal of the posterior fossa with the cervical spine is required the scalp is first separated from the occipital and the temporal bones on each side. A saw-cut is made obliquely through the anterior part of the external auditory meatus and carried forward, parallel, and just anterior to the petrous temporal bone. The saw-cuts from each side meet in the mid-line at the sella turcica.

A skin incision is made from the external occipital protruberance to the mid-lumbar region and the soft tissues are reflected. The cervical spine is freed of lateral muscular attachments. The thoracic and upper lumbar laminæ are sawn through on each side and the strip of tissue containing the laminæ is reflected caudalwards. The thoracic and lumbar cord within its dura is freed by cutting the thoracic and lumbar roots: the lower end of the cord or the cauda equina is transected and the cord and the dura reflected cephalad. A V-shaped saw cut is made through the posterior parts of the upper ribs, meeting in the median plane of the body of the second, third or fourth thoracic vertebra. The lower end and sides of the cervical spine are now free. The neck is flexed and the cut surface of the skull placed on the autopsy table. The upper part of the spine or posterior fossa is freed by sharp

dissection of muscles, ligaments and periosteum on the under-surface of the skull to meet the initial chisel incision or saw-cut. The cervical spine (and posterior fossa) are now free to be removed with the complete spinal cord. In the latter part of the procedure, care must be taken not to deform the cadaver's nose as this can be difficult to disguise.

(*b*) *Reconstruction of the cadaver.*—The thoracic and lumbar laminæ are returned to their normal position and the skin is sutured. The cadaver is turned supine. A length of wood one inch in diameter and one foot in length is cut to fit the thoracic canal into which it is firmly fixed; the upper end projects into the posterior fossa. Plaster-of-Paris bandage is used to seat the stick firmly at its upper and lower ends. Where the posterior fossa has been removed plaster-of-Paris bandages are used to model a new one. The skull and neck are packed with hessian, the skull cap replaced and the skin is sutured.

It is important to ensure that porters and post-mortem attendants responsible for moving cadavers do not "straighten out" a body in which the spine (especially the neck) is flexed, due to some pathological condition of the spine or to rigor mortis. This practice of "straightening out" the spine facilitates transport of the cadaver, but it may also fracture the spine.

(*c*) *The preparation of thin sections* (400–600 *microns*)

(1) *Fixation:* The specimen is fixed in formol-saline for at least two weeks.

(2) *Decalcification:* It is then decalcified in acid (5 per cent nitric acid or 5 per cent hydrochloric acid) for four weeks. The dilute acid solution is changed two or three times and 2½ litres of fluid are used for each change. After the first two weeks the specimen is examined every few days. When the bone feels spongy on compression between finger and thumb it is ready for cutting. Up to 10 per cent acid can be used but then the specimen tends to macerate and must be watched more carefully. A specimen left too long in acid disintegrates when handled. Nitric acid solution acts more rapidly than hydrochloric acid and also colours the tissues in varying shades of amber. This is helpful in differentiating structures in the thin sections. Insufficient decalcification may later ruin the specimen and notch the microtome.

(3) *Washing:* All acid is removed from the specimen by thorough washing. Five to seven days in still water with one or two changes daily and then one or two days in running water is adequate. If the specimen is left in water too long, over three weeks for example, it becomes soggy.

If necessary the specimen can now be stored in formol-saline for an indefinite period. The formol-saline should be changed periodically and must be washed out before embedding.

(4) *Embedding:* The complete specimen or a selected block is placed in warm 25 per cent gelatine solution with the face to be cut uppermost. The block containing the specimen is then mounted on a serrated or grooved plate with 25 per cent gelatine around the base of the block. One to two litres of gelatine solution are used for one complete cervical spine, and it should contain 3 per cent ethylene glycol as an antiseptic. Weak solutions (i.e. less than 20 per cent) cause the formation of large crystals after freezing. This makes cutting more difficult as the crystals tend to separate. When frozen, formolized specimens incompletely washed also tend to produce crystalization of gelatine.

(5) *Freezing:* The gelatine block on the plate is placed in a deep-freeze at −15° C. overnight and removed when ready to cut.

(6) *Cutting:* The plate is set on the microtome and adjusted. The top of the block is wiped with a hot damp rag and the block trimmed down to the specimen by cutting thin sections of the gelatine. On reaching the level at which sections are to be saved, the top of the block is painted with a thin layer of hot 25 per cent gelatine.

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A section at 400–600 microns is then cut, and the top of the block is again painted with hot gelatine and the next section cut; this procedure is repeated to the required level. As each section is cut it tends to roll up so that an assistant is required to hold the forward edge of the section flat while it is being cut. The cut section is then placed on a sheet of wet absorbent paper in a bath of formol saline; another wet sheet of absorbent paper is placed over the section and the second section is placed on top of this and so on. The sections are left in formol-saline for about twenty-four hours.

(7) *Mounting:* Sections are washed in running water for half an hour and then mounted between two sheets of cellophane and backed with a layer of absorbent paper. Each section is numbered and a third sheet of cellophane is placed on the back of the absorbent paper. To mount the section a thin layer of mounting solution (7 per cent gelatine and 7 per cent glycerine in equal parts) is run on to a smooth Perspex plate; the first cellophane sheet is laid in the mounting solution and smoothed out, at the same time any air bubbles are removed. A layer of mounting fluid is run on to the cellophane and the thin section is laid in the fluid: another layer of mounting solution is added and then the second cellophane sheet. The layers of the section are built up with a thin film of mounting solution between each sheet. In each layer it is important to remove the air bubbles.

The plastic plates with the completed sections are then placed horizontally in a stand for half an hour and then hung up in an X-ray film drier overnight. The following day the sections peel off the mounting plate in one piece. If the mounting solution is too dilute the cellophane envelope tends to separate: when this occurs the section and envelope should be placed in warm water and with a little agitation the section can be removed from the cellophane envelope and re-mounted.

(8) *Plane of sections:* Individual specimens or parts of specimens were cut in one of four planes, viz.

(*a*) *Sagittal plane* (fig. 1). Serial sections show the degrees of lordosis, the configuration of the vertebral bodies, the intervertebral discs and the articular columns with the apophyseal joints. About 80 sections can be cut from one specimen and they readily reveal abnormalities of the discs, vertebral bodies and articular columns.

(*b*) *Coronal plane* (fig. 3). The serial sections show the shape of the vertebral bodies, the intervertebral discs, and the articular columns with apophyseal joints. The upward projection on the lateral part of the upper surface of the vertebral bodies, known as the uncus, is particularly well shown. About 50 sections can be cut in this plane.

(*c*) *Oblique plane* (fig. 4). The oblique serial sections are cut in a plane at right angles to the axis of the intervertebral foramina and show the actual size of the foramina and relative position of the nerve roots. About 40 sections can be cut in this plane. These sections are essential for the study of the true size and shape of the intervertebral foramina.

(*d*) *Transverse plane* (fig. 2). Serial sections show the relationship of the spinal cord and nerve roots with their membranes and attachments within the spinal canal. Blocks of about 60 sections can be cut and they show the diameter of the spinal canal at various levels and the soft tissues in the canal and foraminal exists.

Relative Size and Shape of the Cervical Cord and Canal

We encountered more variation in the size of the cervical cord and canal than we had anticipated. Routine autopsy measurements were not made but we were satisfied that the diameters of the canal and the thickness of the cord (and roots) varied independently. Elsberg and Dyke (1934)

found that the interpediculate width of the cervical spine measured on radiographs was approximately 30 mm. Thus,

	C2	C3	C4	C5	C6	C7
Usual upper limits	30	30	32	32	32	31 mm.
Extreme upper limits	31	32	34	33	34	33 mm.

Clear radiographic definition of the cervical pedicles is not readily obtained but in relation to the pathogenesis of cervical myelopathy it is likely that the antero-posterior is more important than the larger transverse diameter of the cervical canal.

Lowman and Finkelstein (1942) measured the *antero-posterior* diameter of the cervical *cord* on lateral radiographs of 80 adults subjected to lumbar air encephalography and found that the maximum average measurement was 10 mm. Arnell (1948; 1951) measured the dimensions of the *cervical intradural space* on opaque myelograms and found that the average *transverse* diameter was 30 mm. and the *antero-posterior* diameter 20 mm. Porter (1956) measured the *transverse* diameter of the cervical *cord* in 65 adults on opaque myelography and found that the average maximum diameter was 14 mm. (10 mm. to 17 mm.).

Wolf, Khilnani and Malis (1956) measured the *A-P diameter* of the cervical *canal* in 200 normal adults. Standard lateral radiographs were used with a tube distance of 72 in. and the A-P diameter opposite each cervical vertebra was recorded. From C3 to C7 the average measurement was 17 mm. They concluded that cord compression was likely to be present when the figure was 10 mm. or less.

We recorded the *antero-posterior* diameter of the *spinal canal* on routine lateral radiographs of 90 adult cervical spines. These comprised three groups of cases. *Group* 1—30 cases, normal cervical spines: *Group* 2—30 cases, cervical spondylosis: *Group* 3—30 cases, cervical spondylosis with myelopathy (viz. paraplegia resulting from the spondylosis). In each group there were 15 males and 15 females. Measurements were made from the posterior border of each vertebral body to the anterior border of the corresponding lamina. At C1 the measurement was taken from the posterior border of the odontoid to the anterior edge of the posterior arch of the atlas. Standard lateral radiographs were used with the patient against the film and a tube distance of 72 in. Table II shows the "mean" and the "range" of the antero-posterior diameters from C1 to C7 in each group.

It will be seen (Table II) that in the *normal* spine there was a range in the antero-posterior measurement frequently amounting to 5 mm. but that the average figure in the lower cervical spine was 17 mm. In *spondylotic* spines the diameter was smaller, especially when there was paraplegia, confirming the evidence of Pallis, Jones and Spillane (1954). In the latter group the smaller measurements were found not only at the levels of the diseased vertebræ and discs but throughout the cervical spine.

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TABLE II.—ANTERO-POSTERIOR DIAMETER OF THE CERVICAL SPINAL CANAL ON RADIOGRAPHS IN 90 ADULTS

	1. Normal				2. Cervical Spondylosis without Paraplegia				3. Cervical Spondylosis with Paraplegia			
	15 Males		15 Females		15 Males		15 Females		15 Males		15 Females	
	Mean mm.	*Range mm.*	*Mean mm.*	*Range mm.*	*Mean mm.*	*Range mm.*	*Mean mm.*	*Range mm.*	*Mean mm.*	*Range mm.*	*Mean mm.*	*Range mm.*
C1	21·8	20·0–26·0	21·6	18·0–24·0	21·0	18·5–23·0	21·2	16·5–24·0	19·6	16·0–25·0	19·3	17·0–24·0
C2	20·2	17·5–23·0	19·8	18·0–22·0	18·3	16·0–20·0	18·5	15·0–21·0	18·1	15·0–21·5	18·2	15·0–21·0
C3	18·8	14·5–22·0	17·9	16·0–20·0	16·3	15·0–18·0	16·4	13·0–18·5	16·0	12·5–21·0	16·1	13·0–18·0
C4	17·6	14·0–20·0	17·3	15·0–20·0	15·5	13·5–18·0	15·3	13·0–17·5	14·6	12·0–18·0	14·7	12·0–18·0
C5	17·8	15·0–22·0	17·1	15·0–19·0	15·0	13·0–18·5	14·8	12·0–16·5	14·4	12·0–17·0	15·0	12·5–17·0
C6	17·8	16·5–20·0	17·0	15·0–18·0	14·7	13·0–17·0	14·8	12·5–16·0	14·1	11·0–17·0	14·5	11·5–17·0
C7	17·8	16·5–20·0	16·6	14·5–18·5	14·9	13·0–18·0	15·1	12·5–17·0	14·4	11·0–17·0	14·6	13·0–17·0

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These observations are by no means conclusive but they do suggest that in cervical spondylosis some reduction takes place in the antero-posterior diameter of the spinal canal and that the development of myelopathy may also be related to the *initial* size of the canal.

In cross section the cervical cord is oval whereas the cervical canal at the level of the pedicles is roughly triangular in shape; the pedicles are directed dorsolaterally (fig. 2, Plate LXVII). This difference in shape in the cervical region produces a space (or recess) of varying size, antero-laterally, between the cord and the wall of the spinal canal. This space is of some practical importance in that (*a*) some reduction of canal size can occur antero-laterally without resulting cord compression, and (*b*) when the spinal cord is compressed anteriorly in the mid-line, the antero-lateral recesses may remain open and continue to serve as a pathway for the flow of cerebrospinal fluid. It is well known that a negative Queckenstedt test does not rule out cord compression in the cervical region, (*c*) during myelography the anterior border of the myodil column in the gutter-like recess may obscure a mid-line protrusion. If the gutter is deep the myodil may slightly overlap the posterior borders of the bodies of the cervical vertebræ. McRae (1956) has pointed out that the layer of oil anterior to the cervical cord is thin and even low protrusions may rise above the central shallow layer of oil.

The Relationship between the Cervical Cord Segments, the Cervical Nerves and the Intervertebral Discs

The anterior and posterior nerve rootlets are attached to the spinal cord in different ways (fig. 8). Each anterior nerve root is formed by the grouping of rootlets which emerge from an elliptical area, the anterior root exit zone, on the anterior surface of the spinal cord. These root exit zones tend to increase in length and approach the mid-line in the lower cervical segments. The posterior rootlets are fatter than the anterior and they enter the spinal cord along the postero-lateral sulcus; their linear extent may be termed the posterior root entrance zone. The latter increase in length in the lower cervical segments and also lie nearer the mid-line, but the convergence is not so marked as in the case of the anterior root exit zones. The inter-root areas are small or absent in the lower cervical cord especially posteriorly.

The normal relationship of the cord segments to the intervertebral discs in the adult cervical spine has not always been clearly represented in anatomical texts. For example, authors differ in their definition of a spinal cord "segment." It may be judged to extend from (*a*) the uppermost fibre of one nerve root to the uppermost fibre of the next adjacent root, or from (*b*) the mid-points of two adjacent inter-root areas, or it may comprise (*c*) the region to which a pair of spinal nerves is attached. We have adopted this definition.

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The intrathecal nerve roots below C3 pass downwards with increasing obliquity to reach their respective intervertebral foramina (fig. 6). At and below the C5 segment this obliquity is sufficient for at least part of the anterior root exit zone to lie at one disc level higher than the foramen through which the radicular nerve leaves the spinal canal. For example, the C7 segment lies opposite the C5–6 disc, whereas the C7 radicular nerve crosses the lateral aspect of C6–7 disc. The corollary of this is that the C6 and C7 nerve roots cross the C5–6 disc.

Similarly, the posterior root entrance zones at and below C 5 segment lie at a higher *laminar* level than their respective intervertebral foramina (fig. 7). The C7 posterior root entrance zone lies opposite the C5–6 apophyseal joint whereas the C7 radicular nerve leaves the spinal canal opposite the C6–7 apophyseal joint.

Statements about the course of the cervical nerves such as the following are in our opinion inaccurate. "In the lower cervical canal . . . the nerves . . . leave the cord almost at right angles" (Bull, 1948). "Each cervical root runs almost transversely across the face of the disc. Compression of two roots by a single protrusion is therefore rare" (Knight, 1948). "These (cervical) nerves unlike those at other levels, pass with their dural sheaths not only horizontally laterally . . ." (O'Connell, 1955).

The dural pouches on the other hand, tend to emerge from the spinal dura at right angles (fig. 9C). Frykholm (1947) has pointed out that the curved course of the lower cervical nerves is guaranteed by the funnel-like shape of these pouches from the bottoms of which the nerves emerge. Fibrosis of the dural sheaths or deformity or absence of a pouch may cause angulation of the corresponding nerve.

Change in these Relationships with Age.—In the fœtus the nerve roots pass transversely to gain exit from the intervertebral foramina. The disproportionate development of the spine relative to the spinal cord results in the roots taking a downward course when adult stature is reached. With advancing years, there is loss of intervertebral disc space and possibly diminution in height of some of the vertebral bodies. Though this loss at any particular level is small, the total effect on spinal height may be considerable. It results in a downward displacement of cervical cord segments in relation to intervertebral disc levels and a reduction in the degree of obliquity of the intrathecal roots.

The clinical significance of these observations is that (*a*) A posterior disc protrusion in the lower cervical spine, if large enough to compress the cord, will also compress part of an anterior root on at least one side.

(*b*) At and below C4–5 disc, a posterior protrusion may affect the nerve root from the next lower segment of the cord; and if there is also constriction of the intervertebral foramen nerve roots from two levels may be involved.

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(*c*) When there is severe narrowing of two or three cervical disc spaces, the cord segments come to lie opposite their respective discs.

The Changes in the Curvature of the Cervical Spine

Probably the commonest gross change seen with age in the cervical spine is the alteration of curvature. In the infant the cervical spine is straight, but with growth, and the full development of the discs, which become thicker anteriorly, a lordosis appears. In middle age the cervical spine tends to become straight again, and thinning of the discs in old age may even render it kyphotic. Exceptionally, there is an actual increase of lordosis in old age.

The Mobility of the Cervical Spine

The movements which take place in the cervical spine are complex; mobility is dependent upon the composite motion between all the vertebræ and not upon the small amount of motion which takes place between any two of them. The head and atlas move essentially as one unit on the axis in rotation and lateral flexion. In nodding movements of the head most of the motion occurs at the atlanto-occipital joints. Generally speaking, stresses and strains are probably greatest in the lower part of the cervical spine. When, as a result of changes in the lower cervical spine, movements are restricted, additional stresses may occur at higher levels in the neck. Fielding (1957) has shown by cineradiographic studies that 90 per cent of neck rotation occurs at the interval between the first and second cervical vertebræ and this is accompanied by approximation of the two segments. In forward flexion the laminæ separate and a gliding movement takes place at the plane joints between the articular facets. The shape and slope of the latter have a considerable influence on the range and variety of movements of the cervical spine as a whole. It is the upward and medial slope of the superior facets which impart a rotary movement during attempts at lateral flexion. A–P radiographs of the neck in rotation and in lateral flexion reveal that these movements cannot occur separately; each is accompanied by the other.

The antero-posterior diameter of the normal cervical canal appears to vary slightly with the position of the neck. In flexion the ligamenta flava are stretched while in extension they are relaxed and bulge forwards reducing the diameter of the canal. This has been shown myelographically by Taylor (1953). Near the skull the ligamenta flava are less tough and elastic and a fuller range of flexion is possible. We removed from three specimens a block of the cervical vertebral bodies, the cord and dura mater, so that the anterior aspect of the ligamenta flava could be studied. On extension of the spine the ligamenta flava protruded forwards, while in flexion they formed a fairly smooth surface with the anterior aspects of the laminæ (fig. 10C and D).

In other fresh specimens we observed the anterior wall of the spinal canal during movements of flexion and extension. A bilateral laminectomy was performed and the cord and dura were removed. In the normal specimen the anterior wall of the canal showed no bulges on flexion or extension. When there was disc degeneration and a tendency to the formation of ridges on the anterior wall of the spinal canal, extension of the spine threw them into greater relief (fig. 10A and B). Nodular protrusions were increased by extension of the spine and sometimes slightly reduced in size on flexion. Movements of the neck probably influence the antero-posterior diameter of the canal in cervical spondylosis and slight flexion of the neck seems to provide the maximum diameter.

Subluxations

Various degrees of antero-posterior displacement of one vertebra or articular column upon another were observed, presumably as the result of laxity of ligaments and capsular structures, following partial displacement of the nucleus pulposus. When the upper vertebra is displaced posteriorly upon the lower, compression of the cord could take place at the postero-inferior lip of the upper vertebra and at the upper edge of the lamina of the lower vertebra. These two points are roughly on the same transverse plane. This type of subluxation is increased by extension of the neck and reduced by flexion. A less common type of subluxation consists in the forward displacement of the upper vertebra. Here, the potential points of compression (the postero-superior lip of the lower vertebra and the lamina of the superjacent vertebra) are at different levels and the cord is better able to adapt itself to the alteration of the curve of the spinal canal. Subluxations may also reduce the vertical and transverse diameters of the intervertebral foramina with resulting cervical root compression and irritation.

The Relationship between the Vertebral Artery and the Cervical Nerves

The second part of the vertebral artery ascends through the foramina transversaria and passes anterior to the anterior primary rami of the cervical nerves (C6–C2) (fig. 5A and C). The artery lies in apposition with each successive nerve, and the nerve sheath is often grooved as the vessel passes upwards. It is conceivable that sclerotic changes in the artery might lead to involvement and scarring of a cervical nerve. The artery may also be kinked or constricted by the osteophytic deformity of the uncus of the vertebral body (fig. 5B). Similar observations have been made by Krogdahl and Torgersen (1940), Haglund (1942), Baacke (1955) and Hutchinson and Yates (1956).

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The Uncus and the "Luschka Joints"

In the adult, on each side of the superior surface of the bodies of the cervical vertebræ, except the first and second, and on the first thoracic vertebra, there is a small bony eminence known as the uncus or uncinate process. It is of variable height on each postero-lateral rim and forms part of the medial wall of the adjacent intervertebral foramen. Above it lies the inferior bevelled edge of the superjacent vertebra. Luschka in 1858 suggested that this lip of bone be called the "eminentia costaria" as it resembled the head of a rudimentary rib. Trolard in 1893 proposed the term "processus uncinatus." Luschka gave a detailed description of the embryology and structure of the intervertebral discs, and of vertical nuclear herniation (now known as Schmorl's nodes). He believed that the intervertebral disc contained a joint cavity and that the *central* intervertebral joint was a synovial or diarthrodial joint. He also found a narrow cavity between each uncus and the inferior "facet" of the superjacent vertebra which contained synovial fluid and was lined by membrane with papillary processes. He considered that these were true *lateral* intervertebral joints and they are usually referred to as "Luschka joints" (fig. 19). He could not always identify them in children and wrote—"in old age, because of a splitting up and changes in the connective tissue of the fibrous ring and nucleus pulposus, a fissure comes into being which can connect the cavities of the lateral joints with the cavity of the central joint . . . The annulus fibrosus does not go round the whole circumference of the vertebra but ends laterally at the point where the lateral joint extends inwards . . . The ease of movement of the neck is not based, as taught to date, on the synchondrosis, but without doubt upon the existence of the lateral joints. Because of the cartilage on the eminentia costaria and on the facet of the vertebra above they can slide readily one upon the other."

A hundred years later opinion remains divided concerning the nature of the lateral fissures described by Luschka. Giraudi (1931) based his conclusion that the joints existed purely on radiological studies and interpreted the unco-vertebral deformity as a manifestation of "arthrosis deformans intervertebralis." The studies of Lyon (1933; 1945) although stressing the clinical importance of the unco-vertebral osteophyte in narrowing the intervertebral foramen did not imply the existence of such lateral articulations between individual cervical vertebral bodies. Rathcke (1934), Guntz (1937) and Tondury (1943) considered that Luschka joints were simple fissures in fibrocartilage but Krogdahl and Torgersen (1940) found that the arrangement of the fibre layers in the lateral part of the annulus and the distinct nature of the outer "capsule-membrane" pointed to the interpretation that the unco-vertebral fissures were a form of articulation. They examined 12 cadaver cervical spines and took care to avoid injury and artefact by filing away, and not cutting, the anterior

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portions of the bodies and discs of some of their specimens. But they wrote "whether it is correct to call these *joints* is doubtful because they lack some of the characteristics of joints." This qualification is overlooked by those who quote Krogdahl and Torgersen as having "demonstrated" Luschka joints. Haglund (1942) studied 40 cadaver cervical spines and concluded that the unco-vertebral fissure was an early sign of disc degeneration: it became continuous with more centrally placed fissures as degeneration progressed. Bull (1948) accepted the descriptions of Luschka and Krogdahl and Torgersen and used the term "neurocentral joints" to designate the "synovial" cavities between the uncus and the superjacent vertebra. He commented on the scant mention they receive in Gray's "Anatomy" where it is said they are "occasionally" present and we confirm that the name Luschka is nowhere to be found in that textbook. Unfortunately the term "neurocentral joint" is there used to describe the primary cartilaginous joint uniting the centrum of each developing vertebra during the first years of life to each half of the vertebral arch. On the other hand, in Frazer's "Anatomy of the Human Skeleton" the joints of Luschka are clearly described and illustrated (diagrammatically). Frazer considers they are in series with the costo-vertebral joints in the thoracic region. Frykholm (1951) whose detailed studies of the cervical spine and nerves are a modern anatomical classic came to the conclusion that it was not justifiable to speak of "unco-vertebral joints." He preferred to speak of the uncinate part of a cervical disc to distinguish it from the main or central portion. The unco-vertebral fissure resulted from stress applied to the thin lateral portion of the annulus. More recently, however, Cave, Griffiths and Whiteley (1955) on the basis of a study of 50 macerated cervical spinal columns and the detailed dissection of a further ten cervical spines wrote that—"Our own studies convince us that the Luschka articulations are constant, normal and necessary features of the cervical spine . . . The joint cavity (which is constant) is limited medially by the periphery of the disc, laterally by a distinct capsular ligament." The commonest cause of cervical root irritation is not, they believe, due to cervical disc degeneration and protrusion but to "osteo-arthritis deformans of the Luschka Joints" with a resulting narrowing of the intervertebral foramina. Moreover, they state, "it is clear that there is no constant correlation between the degree of disc shrinkage and the distribution and severity of neurocentral osteo-arthritis." In her recent monograph Jackson (1956) states that these "lateral intervertebral joints are complete with capsule, synovial lining and articular cartilage" and she too provides diagrammatic illustrations.

Our own studies have led us to precisely opposite conclusions. We have found by careful study of thin sections that an unco-vertebral fissure approximately $3 \times 3 \times 1$ mm. is indeed present in all adult spines (fig. 2A, 3A and B). It was absent only in four infant spines. Synovial membrane was

never detected by histological examination of the uncinate part of the intervertebral discs. It is a mystery to us how Luschka was able to demonstrate fluid in fissures of this size. We do not believe the fissures are solely artefacts due to post-mortem handling but doubt whether they actually exist during life. We consider that they are a result of a separation of annular fibres. The pressure of adjacent vertebræ makes it difficult to imagine that an actual space exists during life. With increasing age they can be identified more readily and they frequently become ragged after middle life and join up with other cracks in the central disc material and the annulus. The peculiar cruciate laminar arrangement of the outer fibres of the annulus fibrosus may predispose to separation of fibres. We have found that a high degree of correlation exists between disc shrinkage and the distribution and severity of unco-vertebral deformity. Despite the statements of Cave and his colleagues referred to above, in the only illustration (fig. 4) in their paper in which both these phenomena can be observed in a single pathological specimen, there is an obvious narrowing and degeneration of the disc opposite the "Luschka joint arthritis." Also, in the X-ray illustration (fig. 16) disc narrowing is present as well as "Luschka joint arthritis."

The explanation for the appearance of unco-vertebral fissuring probably lies in the stress imposed on the lateral parts of the discs as the consequence of the mobility of the cervical spine. To some extent the uncus, by restricting lateral flexion, is protective. But the wide range of movements which are possible occurs at the expense of wear and tear in the uncinate part of the discs where the effects of gliding of one vertebra upon the other are most likely to be felt. Fissuring of fibrocartilaginous material at this site during life could be expected. On the other hand if the unco-vertebral fissures were true lateral synovial joints we would expect them to tend to disappear during life. They are so small that with the passage of time degeneration of the discs would tend to obliterate them and not reveal them.

Elevations on the Anterior Wall of the Spinal Canal

Three types of elevation were seen.

(1) *Lateral elevations* (fig. 9E) were found on the anterior surface of the spinal canal near the intervertebral foramina. They frequently projected into the foramina and were more readily seen after fixation when they were grey-white in colour, of bony hard consistency and lay somewhat obliquely in the spinal canal. They were commonly present at several disc spaces and were usually bilateral. When the dura and ligamentous tissue were removed these elevations were seen to be part of an "everted uncus." They are the commonest type of projection into the spinal canal and tend to spread medially and join in the mid-line to give a low ridge-like appearance. The intrathecal nerve roots cross these lateral elevations

at right angles and in fixed specimens the anterior root is frequently indented. Both roots are here entering the dural root pouch and they may show an upward kinking and fibrosis as described by Frykholm (fig. 9). The spinal cord itself is not affected owing to the lateral position of these elevations. Some degree of disc space narrowing is nearly always present and on lateral radiographs of the cervical spine these elevations may appear as posterior osteophytes; on the radiograph they cannot be distinguished, however, from mid-line posterior osteophytes.

(2) *Transverse ridges* (fig. 12B) in the fresh specimen were commonly seen at one or more disc levels and were usually accompanied by lateral elevations. The ridge extends transversely across the anterior wall of the canal and is formed by:

(*a*) *a fold of annulus* which has become redundant as a result of disc space narrowing,

(*b*) *slight subluxation* of the vertebral bodies, the upper being displaced backwards on the lower,

(*c*) *medial extension of the lateral elevations* (fig. 17).

These transverse ridges reduce the antero-posterior diameter of the spinal canal especially during extension of the neck.

(3) *Nodular protrusions* (fig. 15B) were less frequently seen and were situated at or near the mid-line. The nodes are whitish and firm but can be indented. On rupture a creamy mass may exude, which, on release of pressure partially recedes into the nodule. Extension and flexion of the spine increases and diminishes respectively the size of the protrusion, which in all positions reduces the antero-posterior diameter of the spinal canal. When the spinal cord is fixed *in situ* it may show an indentation on its anterior surface corresponding to a nodular protrusion (fig. 16). The anterior root exit zone on one or both sides is also similarly indented. Nodular protrusions are formed mainly by posterior nuclear displacement, but occasionally they contain an osteophyte from the posterior lip of the superjacent vertebra. They are usually accompanied by lateral elevations and sometimes also by a transverse ridge.

Indentation of the Spinal Cord

Impressions on the *anterior* surface of the spinal cord were commonly seen and corresponded to the shape and position of nodular protrusions and transverse ridges (fig. 13A). These indentations invariably involved at least one anterior root exit zone in the lower cervical cord. Their presence was at first thought to be highly significant but we eventually came to the conclusion that, in some cases at least, they were artefacts produced during fixation. In 18 normal spines there was no abnormality of the cord surface; 5 were examined in the fresh state and 13 after fixation *in situ*. Of 15 specimens with posterior disc protrusions and ridges 10 were fixed *in situ* and 5 were examined fresh. Indentation of the cord

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was noted in each of the 10 cases fixed *in situ* but in only 2 of those examined in the fresh state.

The spinal cord fixed *in situ* takes on the curvature of the spinal canal and any irregularity of the anterior wall of the canal will be impressed on the cord. We have fixed several spinal cords on a corrugated surface and produced anterior impressions. The suppleness of the cord during life, with the play provided by the dentate ligaments and dura, suggests that a posterior protrusion would deflect the cord backwards rather than indent it. If, however, the posterior displacement of the cord is impeded by the laminæ, ligamenta flava or small size of the spinal canal itself then compression of the cord will occur.

In this series of specimens indentation of the *posterior* surface of the cord was rarely observed but when present it corresponded to the adjacent lamina. Except in 2 cases we were not able to find histological changes in the cord underlying anterior indentations.

The Blood Supply of the Spinal Cord

Although the origin, course and mode of branching of the arteries conveying blood to the spinal cord have been recognised for many years the direction and distribution of flow in the vessels are by no means established with certainty. Deductions based solely on arterial injection experiments are unlikely to be conclusive. The anterior spinal "artery" is really a longitudinal anastomotic chain formed by the junction of the terminal ascending and descending branches of the anterior radicular arteries. The most constant of the radicular arteries are those corresponding to the first cervical cord segment but unlike the vessels at lower levels their course is not with the corresponding anterior nerve roots. Although the first anterior radicular artery divides into ascending and descending branches, the ascending limb is very small. The remaining radicular arteries—derived from the vertebral, intercostal, lumbar and sacral arteries—are variable in number and calibre and except for those at C2 enter the spinal canal via the intervertebral foramina. Kadyi (1889) pointed out that in a given specimen there were only six to eight anterior radicular arteries which make a significant contribution to the circulation of the spinal cord. In other words approximately only one-fourth of the spinal nerve roots are accompanied by sizeable radicular arteries. Bolton (1939) concluded from her injection studies that the usual direction of flow in the anterior spinal artery was from above downwards. Above C3 the blood supply was derived from the intracranial portion of the vertebral arteries. From C3 to Th. 1 it came from the cervical portion of those arteries via the anterior and posterior radicular vessels.

We carried out similar injection studies of ten spinal cords but we were not able to come to any firm conclusion concerning the *direction* of blood flow in the cervical portion of the anterior spinal artery. It seemed to us

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that where a large anterior radicular artery joined the anterior spinal chain the flow was not necessarily directed downwards. We thought the blood could also flow in an upward direction. Examination of the disposition of these vessels (fig. 18) certainly suggests this although we agree that the calibre of the various ascending and descending branches do vary. It is conceivable that both the direction and distribution of blood flow in an ascending or descending branch of an anterior radicular artery may be altered when there is an anterior compressing lesion at the appropriate level.

Mair and Druckman (1953) found that the distribution of the lesions within the cord in cervical myelopathy corresponded to that of the field of supply of the anterior spinal artery, except for the sparing, in their 4 cases, of the anterior columns. There was antero-posterior flattening of the cord in each case at the level of compression and they concluded that the anterior spinal artery was compressed, not only on the surface of the cord, but also in its ramifications within the cord. Sparing of the anterior columns was thought to result from the shortness of the supplying branches of the anterior spinal artery and the reduced likelihood of obliterative effect. Girard, Garde and Devic (1954) on the other hand, were unable to conclude, in their 3 cases, that compression of the anterior spinal artery was responsible for the cervical myelopathy. There was no evidence of cord compression but they detected hyaline degeneration of the smaller arterial vessels within the spinal cord. There was no precise topography to these changes and they did not correspond to the field of supply of the anterior spinal artery. Neither were they restricted to the cord segments opposite the spondylotic lesions but were found also in adjacent segments. Similar changes in the vessel walls were observed by Mair and Druckman.

It has not been shown therefore that myelopathy developing in cervical spondylosis is always the result of compression of some part of the anterior spinal arterial chain. We believe that another factor is the antero-posterior diameter of the cervical canal as we have already described.

The Intervertebral Discs

During life the thickness or height of the intervertebral discs can be assessed only by X-ray examination. We have measured the vertical height of apparently normal cervical discs in a series of 25 lateral radiographs and compared them with adjacent vertebral body measurements. In the mid-line the disc to body ratio is usually 1 : 3 to 1 : 2. Similar measurements made on thin sections of normal cervical spines confirm this.

The majority (64) of our specimens were from patients over 40 years of age and most showed changes in the intervertebral discs and adjacent

vertebræ at one or more levels. In the thin sections of normal spines the nucleus pulposus appears as a homogeneous mass bounded by articular cartilage and annulus fibrosus (fig. 1A). The articular cartilage appears more dense than the nucleus pulposus and is sharply delimited from it. The annulus fibrosus, on the other hand, blends with the nuclear material as its individual fibres become less distinct towards the centre of the disc. In some spines in the older age groups the nucleus contained an irregular central cavity approximately 3 mm. in diameter. Discs that showed marked narrowing contained numerous other fissures usually lying in a transverse plane. Some of these connect the lateral or unco-vertebral fissures to the central cavity, both of which are increased in dimension. Other fissures were occasionally observed and were thought to be artefact. In all, 326 intervertebral discs were examined and of these 115 were narrowed. The frequency of involvement of different levels was as follows: C5–6; C6–7; C4–5; C3–4; C2–3; C7–T1. The disc narrowing varied in degree up to almost complete loss of disc height but rarely affected the whole of the cervical spine. In the great majority of narrowed discs there was evidence of nuclear displacement; the nuclear material herniated either vertically through the articular cartilage into the adjacent vertebral bodies or horizontally through a tear in the annular fibres. Some sections showed slight nuclear displacement with multiple disc fissures but with little disc narrowing. A few specimens showed multiple fissuring of all the discs, and each disc although not obviously shrunken was narrower than the average normal disc; in these spines there was also a loss of lordosis. When two spaces were affected they were usually adjacent.

Whether we should regard the cartilage plate as part of the disc or the vertebra is controversial but from the embryological and physiological standpoints the disc and the adjacent parts of the contiguous vertebræ represent a functional unit. The limitation of the epiphysis to the rim of the vertebral body ensures that the entire vertebra is associated with the nutrition of the disc throughout life (Walmsley, 1953).

The Vertebral Bodies

The healthy cervical vertebral body sectioned in the median plane has a "square-cut" appearance (fig. 1B) and even in the coronal plane its peculiar shape cannot fully be appreciated (fig. 3A). The uncus accentuates the transverse concavity of its upper surface; the lower surface is concave in the sagittal plane and convex in the transverse plane. These surfaces give to the intervening disc a peculiar inverted saddle shape which is not perhaps fully appreciated when we speak of "a disc." Its shape no doubt influences the effects of wear and tear. Increased concavity of the anterior and sometimes also of the posterior surfaces of the vertebral bodies adjacent to narrowed discs is a frequent finding. Anterior osteophyte

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formation enhances this concave appearance and the normal "square-cut" appearance is lost (fig. 14D). The vertebral body then appears shorter in height and broader antero-posteriorly (fig. 11C). Normally the trabecular pattern of the cancellous vertebral bodies is evenly distributed: it is contained within a thin shell of compact cortex. Where there is vertical nuclear displacement there is a corresponding area of loss of bone trabeculæ. Adjacent to this osteoporosis the normal trabecular pattern is disturbed and coarser; a "cap" of sclerotic bone frequently overlies the nuclear displacement (fig. 3B). Occasionally we have seen nodes of osteosclerosis within a vertebral body which were unaccompanied by adjacent nuclear displacement. Fusion of the vertebral bodies may occur at points around the rim of the superior and inferior surfaces and then there is considerable disc change and deformity of the vertebral body. Bone trabeculæ may occasionally be seen invading the nucleus via a rent in the articular cartilage.

We subscribe to the view that as with other tissues there must be a normal (physiological) ageing process for the vertebral column and that morphological and radiological alterations are not necessarily manifestations of disease (pathological). Macro-radiography and histo-radiography of vertebral columns in ageing man and dog has shown that the ageing process follows along approximately similar lines in spite of the fact that the canine vertebræ do not support the weight of the body (Bohatirchuk, 1955). Cord compression may occur in the dog as a result of disc protrusion and some species (e.g. Dachshund) are especially prone to paralysis from this cause (Vaughan, 1956). In man Bohatirchuk found that hypertrophic as well as atrophic changes occurred in the bodies of the vertebræ of the ageing spine and we have been impressed by the degree of change often to be found in association with disc degeneration. In some cases the macroscopic changes within the bodies of affected vertebræ resemble carcinomatous deposits (fig. 13B).

The Intervertebral Foramina

The foramen formed by the apposition of the vertebral notches of two adjacent cervical vertebræ is in reality a short canal about 4 mm. long (fig. 4). The length of the canal, its direction and position depend upon the breadth, inclination and position of the adjacent pedicles. Although it varies slightly at different levels in general the foramina are directed anteriorly, laterally and inferiorly; in the lower cervical region the downward and outward slope tends to increase.

The position of the canal in relation to the adjacent intervertebral disc is variable: in the upper cervical spine the central axis of the canal lies mainly above the disc, whereas in the lower cervical spine it lies at or below disc level. The boundaries of the canal are formed by the inferior and superior surfaces of the adjacent pedicles; posterolaterally, by the

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medial aspect of the apophyseal joint and the adjacent part of the articular columns; anterolaterally, the wall of the canal is formed by the postero-lateral aspect of the uncus, the intervertebral disc and the inferior part of the superjacent vertebræ.

In vertical section the canal is oval or egg-shaped, the vertical diameter being approximately twice the horizontal. The average vertical diameter is 10 mm., the transverse diameter 5 mm.

Nerve roots and vessels traverse the canal. In the cervical region these structures lie nearer the upper pedicle at the medial end of the canal, while laterally they lie nearer the lower pedicle. Movement may result in friction of nerve fibres at these points. In the canal the anterior nerve root lies anterior and inferior to the posterior root. Occasionally the proximal part of the posterior root ganglion lies in the lateral end of the canal. The dural root pouch projects into the foramen and then continues as the peri-neural investment of the radicular nerve. This blends with the peri-radicular fibrous tissue which is the lateral extension of the posterior longitudinal ligament. Further laterally this continues as a fibrous investment of the vertebral artery. Loose areolar and fatty tissue with a venous plexus fill the remainder of the intervertebral canal. Swanberg (1915) was one of the first to study the detailed anatomy of the intervertebral foramina and he noted that the most abundant constituent is fatty tissue. The semi-fluid condition of this tissue during life, he considered, was an admirable arrangement for the protection of the contained nerve.

The lateral spinal arteries derived from the vertebral artery pass medially and where they continue as an anterior or posterior radicular artery, they quickly gain their respective root and pass through the canal with it. The relative size of the nerve to the intervertebral foramen is usually said to be 1 : 3 to 1 : 5. From our oblique sections we estimate that the ratio varies from 1 : 2 to 1 : 8. The foramen between C2–3 is the largest but it is traversed by the smallest radicular nerve. Theoretically the vertical diameter of the foramen should be increased by flexion of the cervical spine and decreased during extension.

In this series of cases narrowing of the intervertebral foramina was a common finding. With increasing age it was more conspicuous and the number of foramina involved increased. The commonest cause of narrowing was from the formation of unco-vertebral osteophytes which were invariably associated with narrowing of adjacent intervertebral discs. Some intervertebral foramina were narrowed by osteophytes from the inferior facet of the apophyseal joints. A few cases showed that postero-lateral herniation of the nucleus pulposus was responsible for the narrowing. These factors were frequently combined.

Thin sections probably present the only method whereby the exact relationship of nerve roots to the foramina can be judged. Constriction

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of a foramen is sometimes accompanied by deformity of the radicular nerve, especially the posterior nerve root; the anterior nerve root often avoids compression by lying in a niche under the deformed uncus. This perhaps explains the relative infrequency of lower motor neurone phenomena in cervical spondylosis.

The Articular Columns and the Apophyseal Joints

Each articular column is about the same height as the body of the vertebra. In transverse section it forms about a quarter of the vertebral body surface. The articular columns are separated from each other by true synovial apophyseal joints which frequently showed osteophytes at one or more levels in the cervical spine. At the affected joints the articular cartilage was pitted or denuded while the adjacent bone showed sclerosis or eburnation with disturbance of the joint surface. Partial or complete fusion sometimes occurred at these joints. In subluxation some overlapping of the surfaces of the apophyseal joints may be found.

Arthritis of the apophyseal joints is not nearly as common as disc degeneration. Changes in these joints are by no means an inevitable accompaniment of age and they are frequently unaffected in cervical spondylosis. This difference in the incidence of "degeneration" between the intervertebral joints and the apophyseal joints is probably significant when one considers the ætiology of cervical spondylosis. If the latter were a manifestation or sequel of arthritis of "Luschka joints" we might expect to find a greater incidence of "apophyseal arthritis" in spondylotic spines. Such is not the case.

Summary and Conclusion

(1) The Gough-Wentworth technique for preparing thin sections of entire organs mounted on paper has been used to study the cervical spine. 70 autopsies provided the material.

(2) Particular attention has been paid to anatomical features which may be significant in relation to the nature and pathogenesis of the neurological sequelæ of cervical spondylosis.

(3) Variation in the size of the cervical cord and canal; the oblique course of the lower cervical nerves; the failure to identify the "Joints of Luschka" are among the observations made.

(4) The alterations that may take place during life in the relationships between the intervertebral discs, the cervical nerves and the cervical cord segments are described.

(5) Cervical spondylosis is not synonymous with cervical osteoarthritis if by the latter term is meant an affection of the synovial joints of the cervical spine. The so-called "Luschka joints" are no more than unco-vertebral fissures in the lateral parts of the cervical discs. There is

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no particular correlation between arthritis of the synovial apophyseal joints of the cervical spine and disc degeneration. Nevertheless the changes that take place in cervical spondylosis resemble those seen in osteo-arthritis of synovial joints. Although there is considerable structural difference between an intervertebral disc and a synovial joint the source and mode of nutrition of the articular cartilage in each case may have much in common.

(6) Cervical spondylosis is primarily a degenerative process affecting the vertebral bodies and the intervertebral discs. The cause of this degeneration is not known but as the nutrition of the disc is derived from the marrow of the vertebral bodies it is possible that a failure of diffusion occurs. Considerable alteration takes place in the shape and texture of the bodies of the vertebræ in many cases of cervical spondylosis. Defects in the cartilage plates allow nuclear displacement into the cancellous tissue of the bodies of adjacent vertebræ. By the thin section technique it can be shown that partial nuclear displacement is nearly always present when the disc is narrowed. The resulting approximation of the bodies of adjacent vertebræ leads to deformity of the uncus, marginal lipping, partial occlusion of the intervertebral foramina and ridge formation on the anterior wall of the spinal canal, Herniation of disc material through tears in the annulus is commonly associated with these changes.

(7) The cervical nerves may be kinked or compressed as the result of the changes taking place in the neighbourhood of the intervertebral foramina. Compression of the roots and indentation of the cord were also observed opposite ridges on the anterior surface of the spinal canal. We concluded however that some of the indentations were artefacts produced when the cord was fixed *in situ*. Histological signs of cord degeneration in relation to these indentations were observed in only two cases. Whether the ridges on the anterior surface of the cervical canal will compress the cord depends to some extent on the relative dimensions of the cord and the canal. These do vary. The average antero-posterior diameter of the spinal canal on standard radiographs from C4 to C7 is 17 mm. and in myelopathy due to cervical spondylosis the average measurement is smaller (about 14 mm.). Spondylotic changes may reduce the canal size but myelopathy is more likely to occur when the original dimensions of the canal are smaller than the average.

(8) Interference with the anterior radicular and anterior spinal arteries is also a likely factor in the production of myelopathy. The anterior spinal artery is a very variable structure—a longitudinal anastomotic chain rather than a mid-line trunk with lateral branches. Alterations in the flow and distribution of blood to segments of the cervical cord may be associated with the changes in spondylosis.

(9) A "corrugated" appearance of the anterior border of a column of myodil in the spinal canal in cervical spondylosis may be exaggerated by the depth of the antero-lateral recesses. The influence of the movements

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of flexion and extension on the appearance of the myodil column should always be considered in interpreting any "defect."

(10) The maximum antero-posterior diameter of the cervical canal in cervical spondylosis with ridge formation is provided by the position of slight flexion. Immobilization of the neck in the "chin-up" position is contra-indicated; the best position is with the neck slightly flexed and the chin "tucked in."

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REFERENCES

BAACKE, H. H. (1955) *Fortschr. Rontgenstr.*, **82,** 482.
BOHATIRCHUK, F. (1955) *Brit. J. Radiol.*, **28,** 389.
BOLTON, B. (1939) *J. Neurol. Psychiat.*, **2,** 137.
BULL, J. W. D. (1948) *Proc. R. Soc. Med.*, **41,** 509.
CAVE, A. J. E., GRIFFITHS, J. D., and WHITELEY, M. M. (1955) *Lancet*, i, 176.
ELSBERG, C. A., and DYKE, C. G. (1934) *Bull. neurol. Inst. N.Y.*, **3,** 359.
FIELDING, J. W. (1957) *J. Bone Jt. Surg.*, **39A,** 1, 222.
FRYKHOLM, R. (1947) *J. Neurosurg.*, **4,** 403.
—— (1951) *Acta chir. scand.*, **101,** 345.
—— (1951) *Acta chir. scand.*, Suppl. 160.
GIRARD, P. F., GARDE, A., and DEVIC, M. (1954) *Rev. neurol.*, **90,** 48.
GIRAUDI, G. (1931) *Radiol med., Torino*, **18,** 1457.
GOUGH, J., and WENTWORTH, J. E. (1949) *Proc. 9th Internat. Cong. Industr. Med.* (1948), p. 661.
GUNTZ, E. (1937) *Z. Kruppelfurs.*, **30,** 84.
HAGLUND, F. (1942) *Acta radiol., Stockh.*, **23,** 568.
HUTCHINSON, E. C., and YATES, P. O. (1956) *Brain*, **79,** 319.
JACKSON, R. (1956) The Cervical Syndrome, Springfield, Ill.
KADYI, H. (1889) Quoted by Bolton.
KNIGHT, G. C. (1948) *Proc. R. Soc. Med.*, **41,** 511.
KROGDAHL, T., and TORGERSEN, O. (1940) *Acta radiol., Stockh.*, **21,** 231.
LOWMAN, R. M., and FINKELSTEIN, A. (1942) *Radiology*, **39,** 700.
LUSCHKA, H. von (1858) Die Halbgelenke des menschlichen Korpers, Berlin.
LYON, E. (1933) *Fortschr. Rontgenstr.*, **48,** 46.
—— (1945) *J. Bone Jt. Surg.*, **27,** 248.
MCRAE, D. L. (1956) *Acta radiol., Stockh.*, **46,** 9.
MAIR, W. G. P., and DRUCKMAN, R. (1953) *Brain*, **76,** 70.
O'CONNELL, J. E. A. (1956) *Proc. R. Soc. Med.*, **49,** 202.
PALLIS, C., JONES, A. M., and SPILLANE, J. D. (1954) *Brain*, **77,** 274.
PORTER, E. C. (1956) *Amer. J. Roentgenol.*, **76,** 270.
RATHCKE (1934) *Dtsch. Z. Chir.*, **242,** 122.

XUM

SWANBERG, H. (1915) *N.Y. Med. Rec.*, **87**, 176.
TAYLOR, A. R. (1953) *Lancet*, **1**, 717.
TONDURY, G. (1943) *Z. Anat. Entw.Gesch.*, **112**, 448.
TROLARD (1893) *Int. Monatschr. F. Anat. Physiol.*, **10**, 3.
VAUGHAN, L. (1956) Personal communication.
WALMSLEY, R. (1953) *Edinb. med. J.*, **60**, 341.
WOLF, B. S., KHILNANI, M., and MALIS, L. (1956) *J. Mt. Sinai Hosp.*, **23**, 283.

LEGENDS FOR PLATES

PLATE LXVI

FIG. 1.—*Sagittal sections* (400 *to* 600 *microns*) *of cervical spines at different ages.* A, second decade; B, third decade; C, fifth decade; D, sixth decade; E, seventh decade; F, eighth decade. Note gradual loss of lordosis and ultimate kyphosis.

PLATE LXVII

FIG. 2.—*Transverse sections of cervical spine.* A, through lower part of body of C5, just shaving the intervertebral disc, and passing through intervertebral foramen. Note the unco-vertebral fissure, posterior root ganglia, vertebral arteries, apophyseal joints, dura and ligamenta flava. B, through pedicles and lower part of intervertebral disc (C5–6). Section passes through base of uncus. Note tiny lateral ligaments of the dura. In both these sections the oval shape of the cord and the triangular shape of the spinal canal can be seen. Myodil in a deep antero-lateral recess or gutter may accentuate a trivial protrusion in the mid-line.

PLATE LXVIII

FIG. 3.—*Coronal sections of a cervical spine.* A, note thickness of discs and concave upper surface of bodies of vertebræ. B, showing relationships of the intervertebral foramina and nerves to the discs and the apophyseal joints. There is vertical (downward) displacement of disc material into the body of the seventh cervical vertebra. C, showing articular columns and apophyseal joints. Note obliquity of C8 nerve as it leaves the cord.

PLATE LXIX

FIG. 4.—*Oblique sections of cervical spine.* A, parallel to cervical nerves as they pass through the intervertebral foramina. B, through intervertebral foramina to show relationships between nerves, discs and apophyseal joints.

PLATE LXX

FIG. 5.—*The vertebral artery in the cervical spine.* A, dissection of left antero-lateral aspect of cervical column showing relationship of the vertebral artery to the cervical nerves as they emerge in the gutters of the transverse processes. B, vertical oblique section through the posterior root ganglia showing compression and distortion of the vertebral artery by an unco-vertebral osteophyte. C, parasagittal section through a vertebral artery showing an intervertebral disc bulging slightly into the lumen of the artery. Serial sections showed that the artery at this point was compressed and narrowed.

XUM

PLATE LXXI

FIG. 6.—*Sagittal section in median plane* with cervical cord reflected. Note increasing obliquity of lower cervical nerve roots.

FIG. 7.—*Dissection exposing right postero-lateral aspect of the cervical cord* showing obliquity of cervical roots and nerves as they enter the intervertebral foramina. Each nerve is nearer the upper pedicle at the entrance and nearer the lower pedicle at the exit from the foramina.

PLATE LXXII

FIG. 8.—A, *anterior surface of cervical cord* to show manner in which the anterior roots emerge from the cord. The root exit zones are elliptical in shape and increase in length and converge towards the mid-line as we descend the cord. B, *posterior surface of cervical cord.* The posterior roots are fatter and they enter the cord along the postero-lateral sulcus. Convergence is less marked. On both aspects of the cord, in the lower cervical segments, especially posteriorly, the inter-root areas become smaller.

PLATE LXXIII

FIG. 9.—*Radiographs and dissections from a case to show implication of a cervical nerve* (C6) *as the result of a disc lesion* (C5–6). Anterior and oblique radiographs (A and B) show constriction of C5–6 intervertebral foramen on the right side by encroachment of an unco-vertebral osteophyte. In C and D we see the deformity of the sixth cervical nerve—before and after resection of dura. In E we are looking at the intervertebral foramina from the *inner* aspect; note how the unco-vertebral osteophyte, which has developed as a result of disc narrowing, projects into the C5–6 foramen.

PLATE LXXIV

FIG. 10.—*Dissections of specimens with moderate spondylosis showing anterior* (A *and* B) *and posterior* (C *and* D) *surfaces of the cervical canal and the effects of extension.* In A the spine is in the neutral position. In B it is being hyperextended; note ridge formation on anterior surface of canal. Similarly, in C and D we see how hyperextension throws the ligamenta flava into folds. When the capacity of the cervical canal is reduced by ridge formation in cervical spondylosis the neck should not be immobilized in hyperextension. The best position is with the neck slightly flexed and chin "tucked in."

PLATE LXXV

FIG. 11.—*Radiograph* (A)*; Anterior surface of cervical canal,* (B)*; Sagittal section of cervical spine,* (C)*; Anterior surface of the cervical cord,* (D)*; all from the same specimen.* On radiograph note the disc narrowing, marginal sclerosis, anterior and posterior osteophytes at C5–6 and C6–7 and alteration of shape of bodies of C5 and C6. In B there is corresponding ridge formation on the anterior surface of the spinal canal. In C there is characteristic alteration of the contour of the bodies of the fifth, sixth and seventh cervical vertebræ with disc degeneration. In D is seen the anterior surface of the spinal cord which was fixed *in situ.* The indentations at C5, C6 and C7 are artefacts. There were no histological changes in the spinal cord and no history of paraplegia.

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PLATE LXXVI

FIG. 12.—*Radiograph* (A)*; Anterior surface of cervical canal* (B)*; Sagittal section of spine* (C)*; Lateral aspect of cervical cord* (D)*; same specimen.* Radiograph shows narrowing of C4–5, 5–6, 6–7 disc spaces with characteristic alteration of contour of adjacent vertebral bodies. In B there is corresponding ridge formation on anterior surface of spinal canal (dura reflected). Sagittal section (C) shows gross degree of change in bodies of fifth and sixth cervical vertebræ with loss of discs. Indentation of anterior surface of spinal cord can be seen in D.

PLATE LXXVII

FIG. 13.—*Specimen* showing (A), anterior surface of spinal canal with ridge formation and slight impressions on anterior surface of the spinal cord which was fixed *in situ.* In B and C the extent of the degeneration of the bodies and discs may be seen. There is replacement of the cancellous tissue of the third, fourth and fifth vertebræ by compact bone. Such changes may superficially resemble metastatic carcinoma.

PLATE LXXVIII

FIG. 14.—*Specimen showing Radiograph* (A)*; Anterior surface of spinal canal* (B)*; Anterior surface of cervical cord* (C)*; Thin sagittal section of cervical spine* (D). We see the disc narrowing and foraminal constriction; the ridge formation on the anterior surface of the cervical canal; the cord compression at C6 with obliteration of the anterior spinal artery; the characteristic alteration (loss of height and increased A–P diameter) of the bodies of the fourth, fifth and sixth cervical vertebræ with corresponding disc degeneration.

PLATE LXXIX

FIG. 15.—*Radiograph, cervical spine and spinal cord from a patient with cervical spondylosis and myelopathy of nine years' duration.* A, radiograph showing signs of a lesion of C5–6 disc. B, anterior surface of spinal canal with a single ridge at C5–6 disc level. C, thin sagittal section to show condition of affected disc. D, vertical oblique section through intervertebral foramina to show constriction of C5–6 foramen and compression of C6 nerve. E, lateral view of spinal cord before fixation showing constriction at C6–7. F, transverse section of spinal cord at C6–7 showing effects of compression by disc lesion. G, cord section at Th.3 to show degeneration of crossed pyramidal tracts. H, cord section at C2 to show demyelination in posterior columns.

PLATE LXXX

FIG. 16.—*Anterior surface of cervical cord* showing small indentation in the mid-line involving C6 anterior roots. The cord was fixed *in situ*; the indentation was produced by a C4–5 disc protrusion. In similar cases when the spinal cord is removed *before* fixation there is usually no indentation. When the spinal cord is fixed *in situ* any irregularity on the anterior surface of the cervical canal will make an impression on the spinal cord. It does not follow therefore that an indentation such as this signifies that there was cord compression during life.

FIG. 17.—Posterior aspect of junction of bodies of fifth and sixth cervical vertebræ showing how a transverse ridge may be formed by marginal lipping.

XUM

PLATE LXXXI

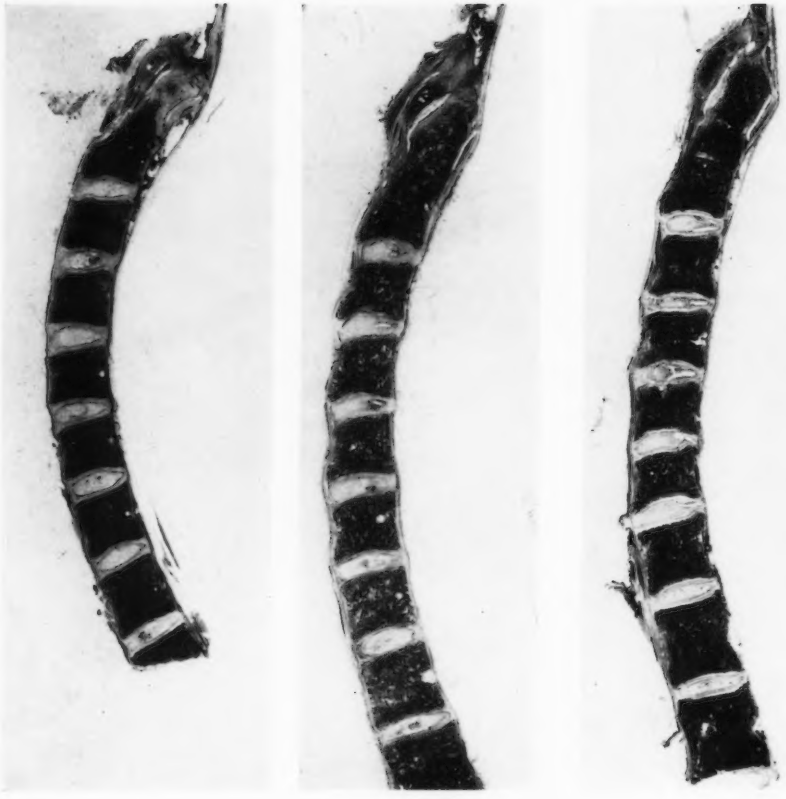
FIG. 18.—*The anterior spinal artery.* This is really a longitudinal anastomotic chain formed by the division of the anterior radicular arteries near the mid-line into ascending and descending branches. Derived from the vertebral, intercostal and lumbar arteries, the anterior radicular arteries are very variable in number and enter the spinal canal via the intervertebral foramina. In A the injected arteries (the dark vessels are the veins) show that on the left side there are anterior radicular vessels at C4, C5 and C8. On the right side only at C6 and C7. In B and C a filter has been used in photographing the specimen so that the veins are not revealed. The variability of the arterial pattern and number of anterior radicular arteries is demonstrated.

PLATE LXXXII

FIG. 19.—This is the original illustration used by Luschka in 1858 in his "*Die Halbgelenke*" to demonstrate the "*Hemiarthrosis intervertebralis lateralis*" (B). Since termed the "Luschka joints" or the "Neurocentral joints" we have come to the conclusion that they are not "joints" but small fissures in the unco-vertebral portion of the intervertebral discs.

Sagittal section of adult cervical spine

PLATE LXVI

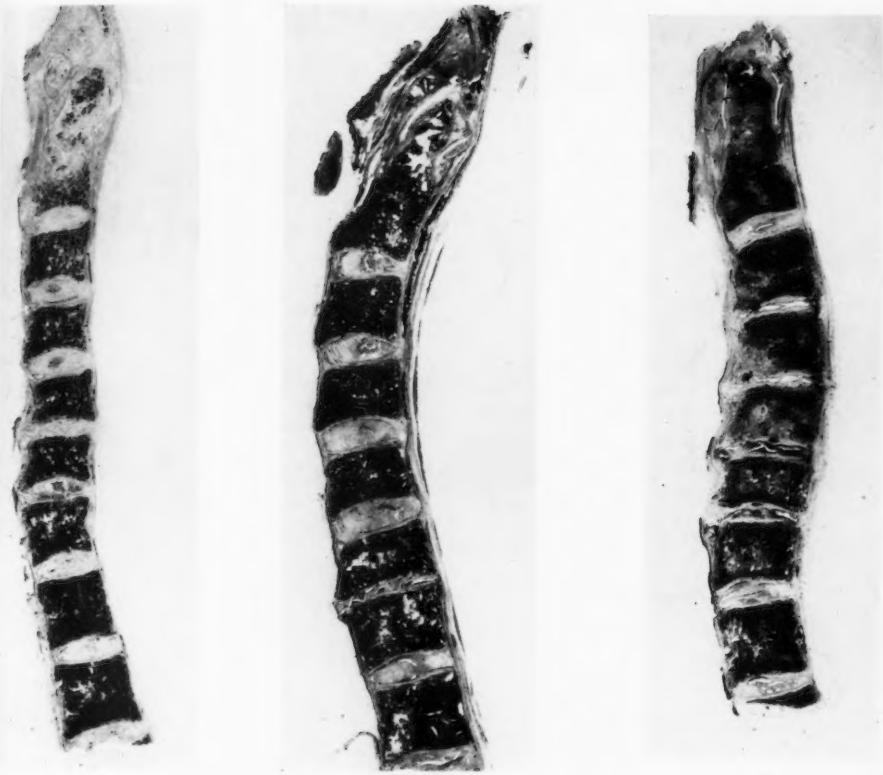


A B C

FIG. 1.

To illustrate article by Eric E. Payne and John D. Spillane.

PLATE LXVI (*continued*)

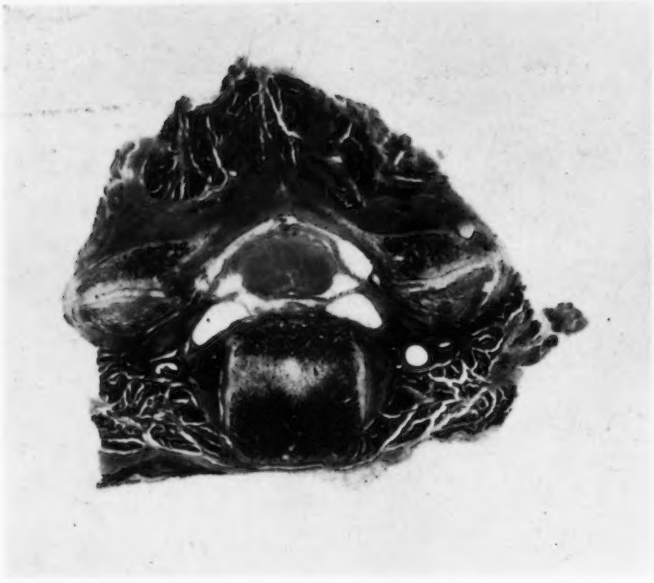


D E F

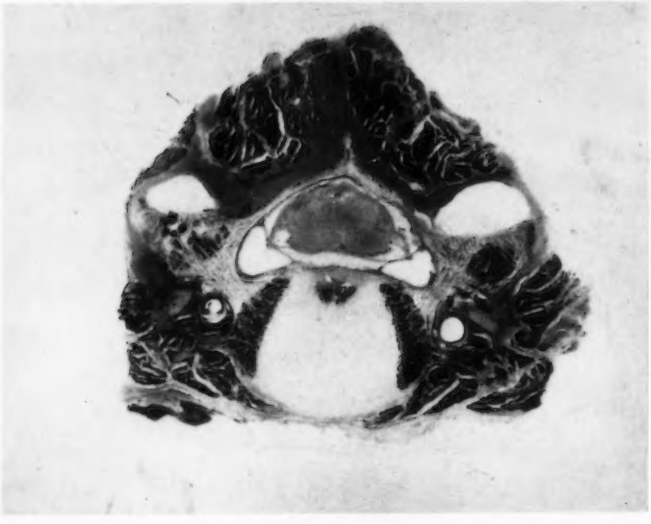
FIG. 1 (*continued*)

To illustrate article by Eric E. Payne and John D. Spillane.

PLATE LXVII



A



B

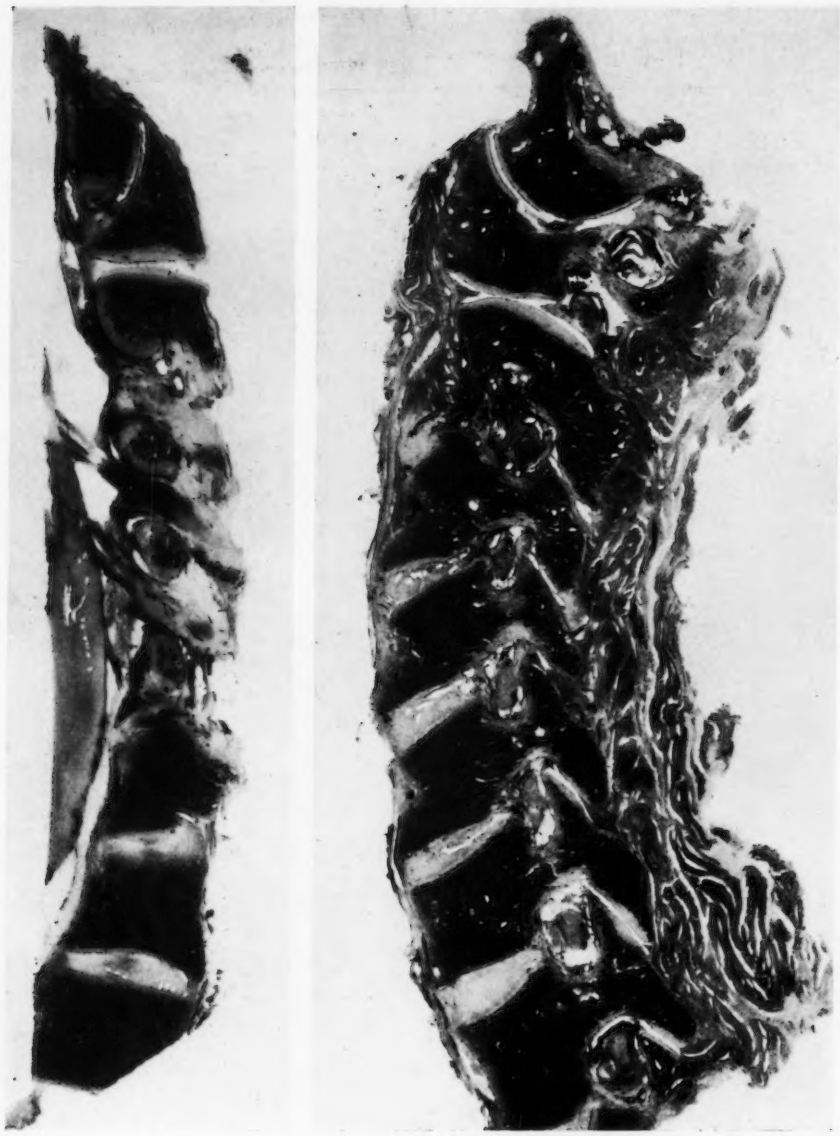
FIG. 2.

To illustrate article by Eric E. Payne and John D. Spillane.

FIG. 3.

To illustrate article by Eric E. Payne and John D. Spillane.

PLATE LXIX



A B

FIG. 4.

To illustrate article by Eric E. Payne and John D. Spillane.

A

C

B

FIG. 5.

To illustrate article by Eric E. Payne and John D. Spillane.

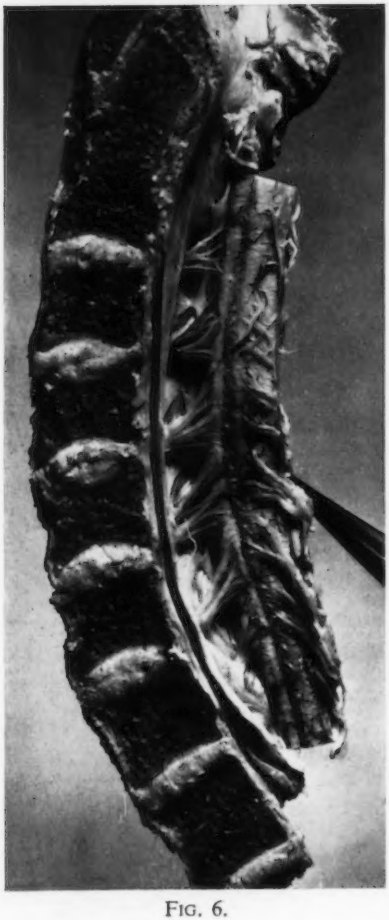


FIG. 6.

FIG. 7.

To illustrate article by Eric E. Payne and John D. Spillane.

A FIG. 8. B

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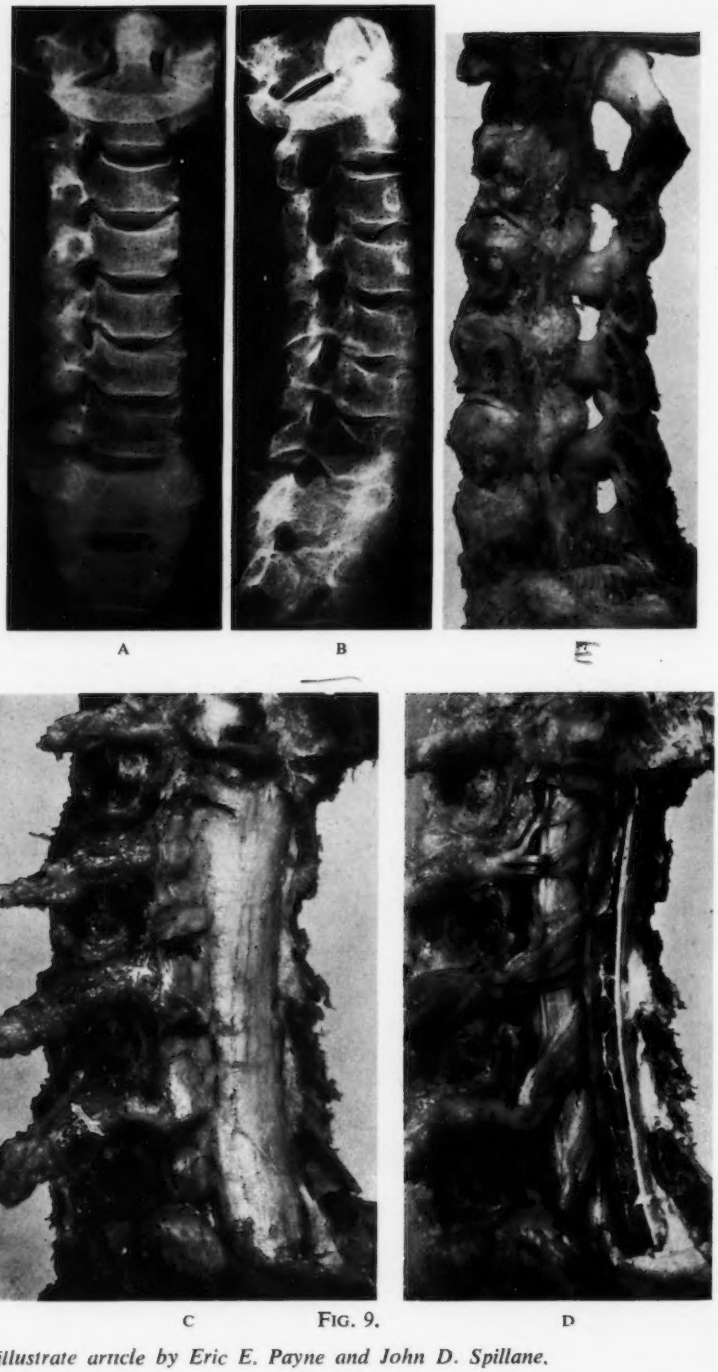
PLATE LXXIII

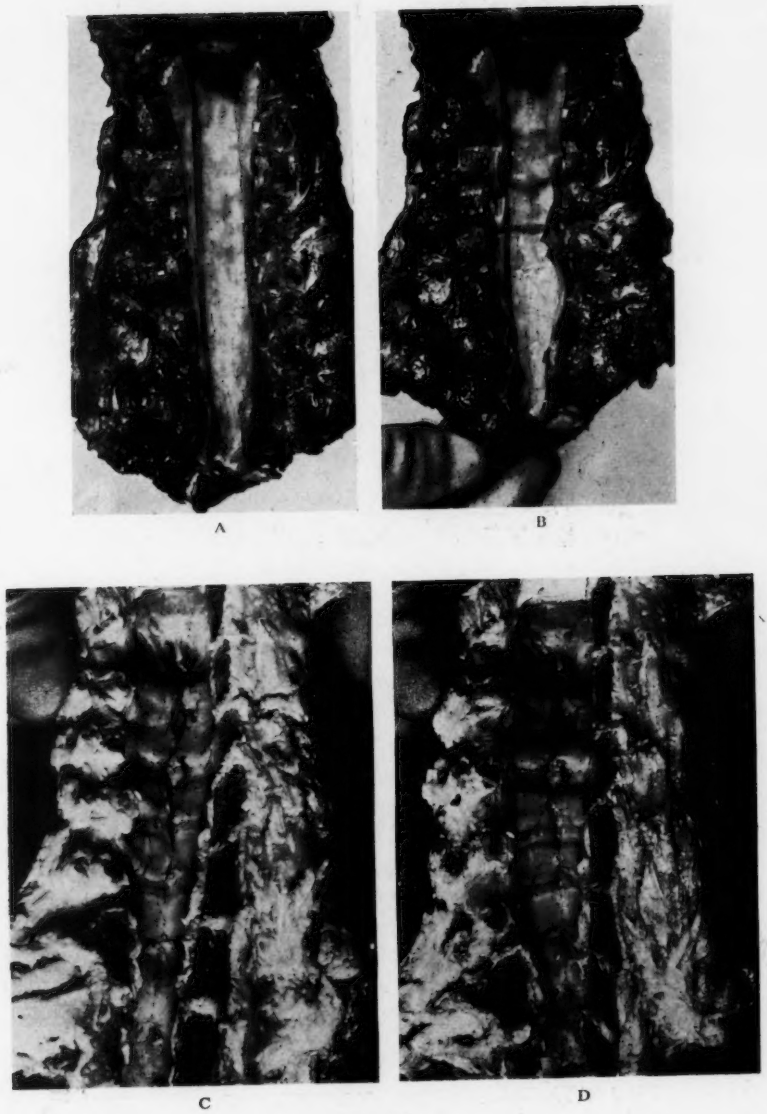


A B C D

FIG. 9.

To illustrate article by Eric E. Payne and John D. Spillane.

PLATE LXXIV



A B C D

FIG. 10.

To illustrate article by Eric E. Payne and John D. Spillane.

PLATE LXXV

A

B

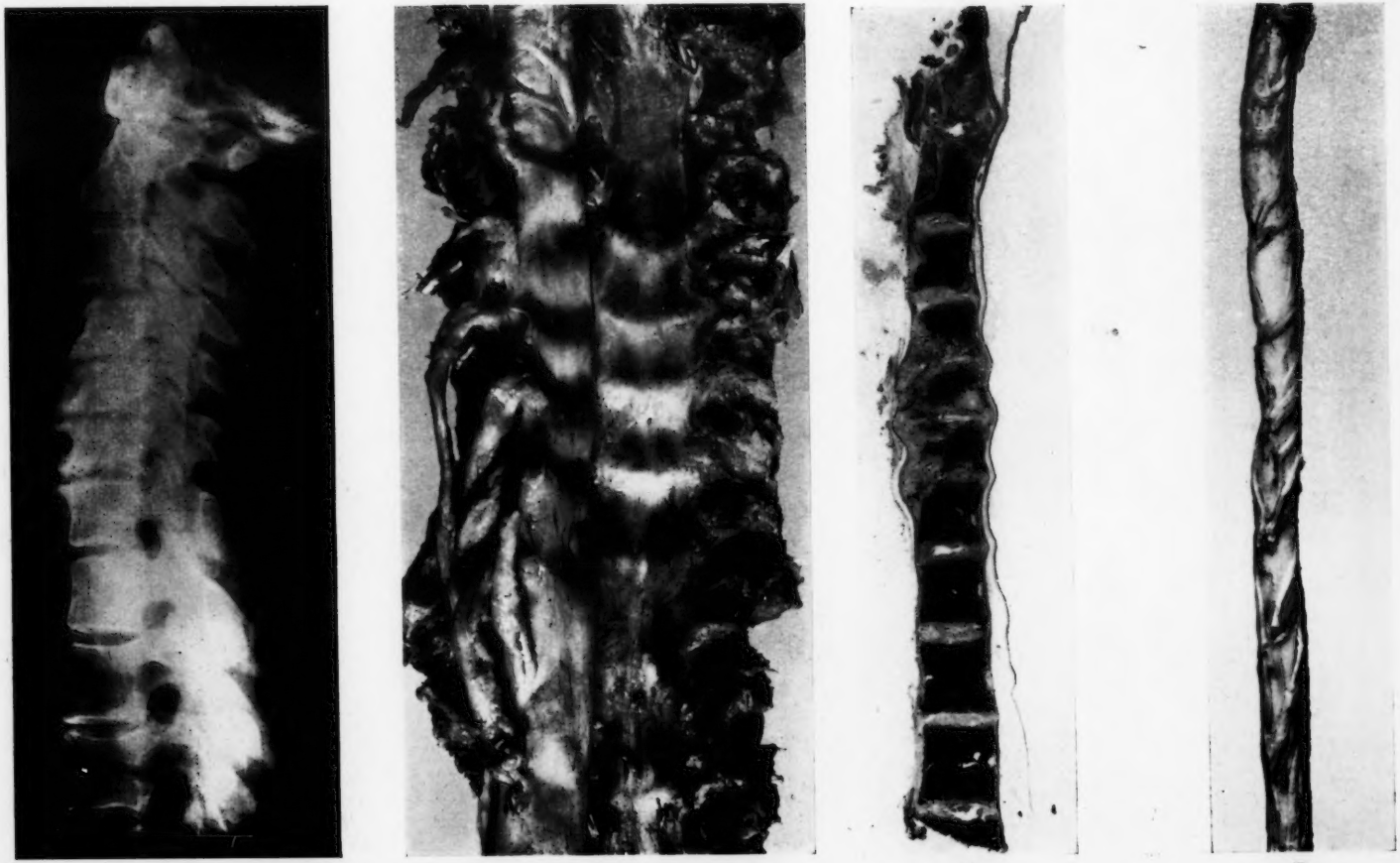
C

D

FIG. 11.

To illustrate article by Eric E. Payne and John D. Spillane.

PLATE LXXVI

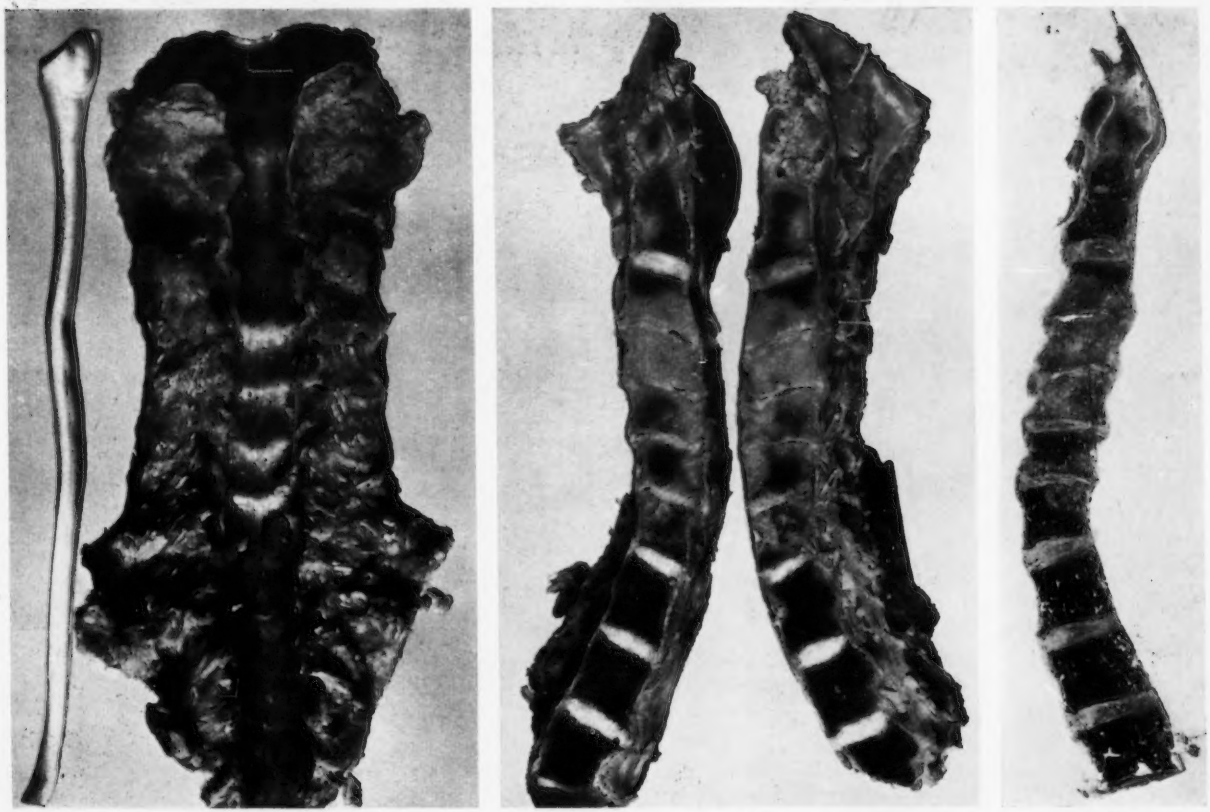


A B C D

FIG. 12.

To illustrate article by Eric E. Payne and John D. Spillane.

PLATE LXXVII



A B C

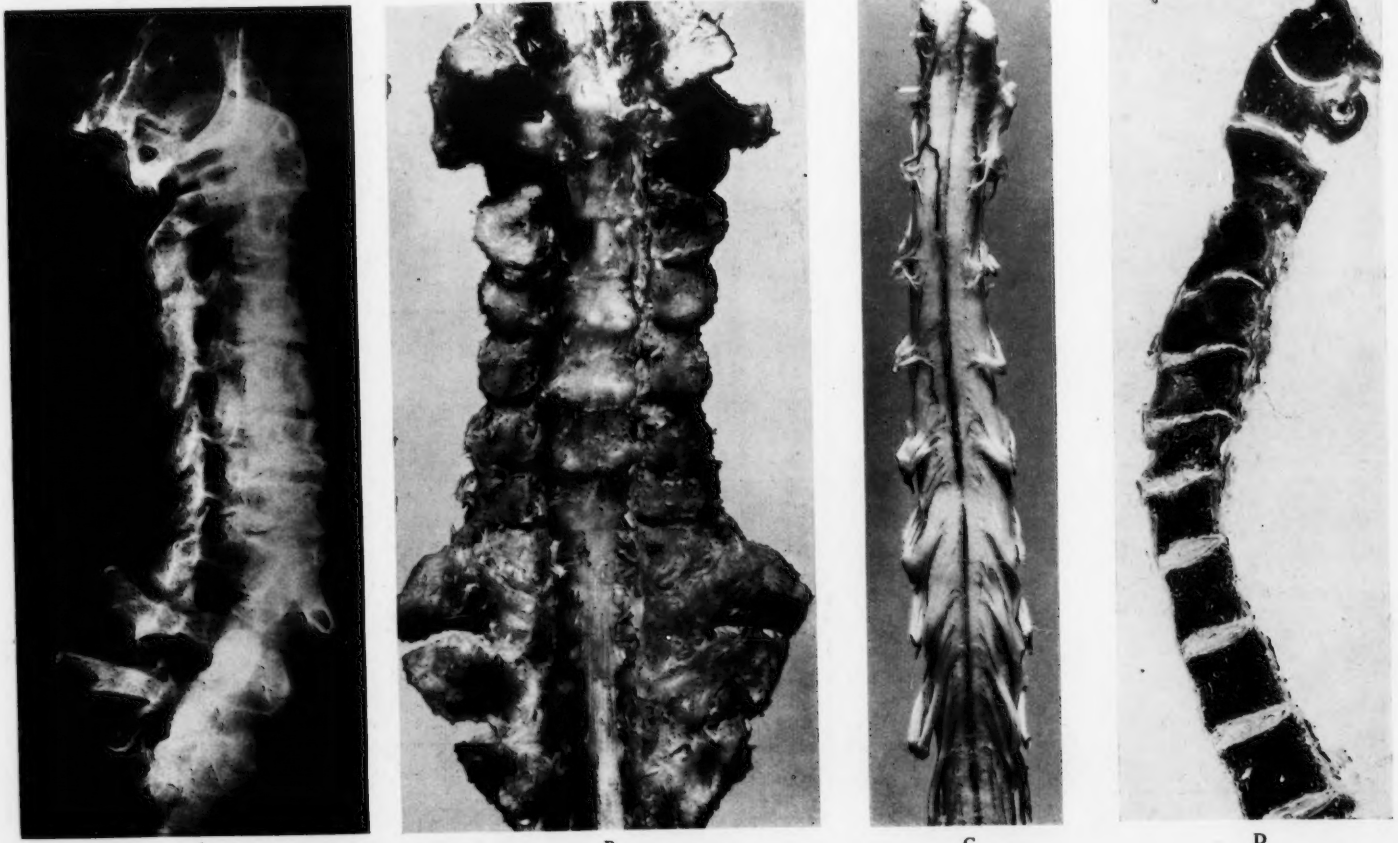
FIG. 13.

To illustrate article by Eric E. Payne and John D. Spillane.

FIG. 13.

To illustrate article by Eric E. Payne and John D. Spillane.

PLATE LXXVIII



A B C D

FIG. 14.

To illustrate article by Eric E. Payne and John D. Spillane.

PLATE LXXIX

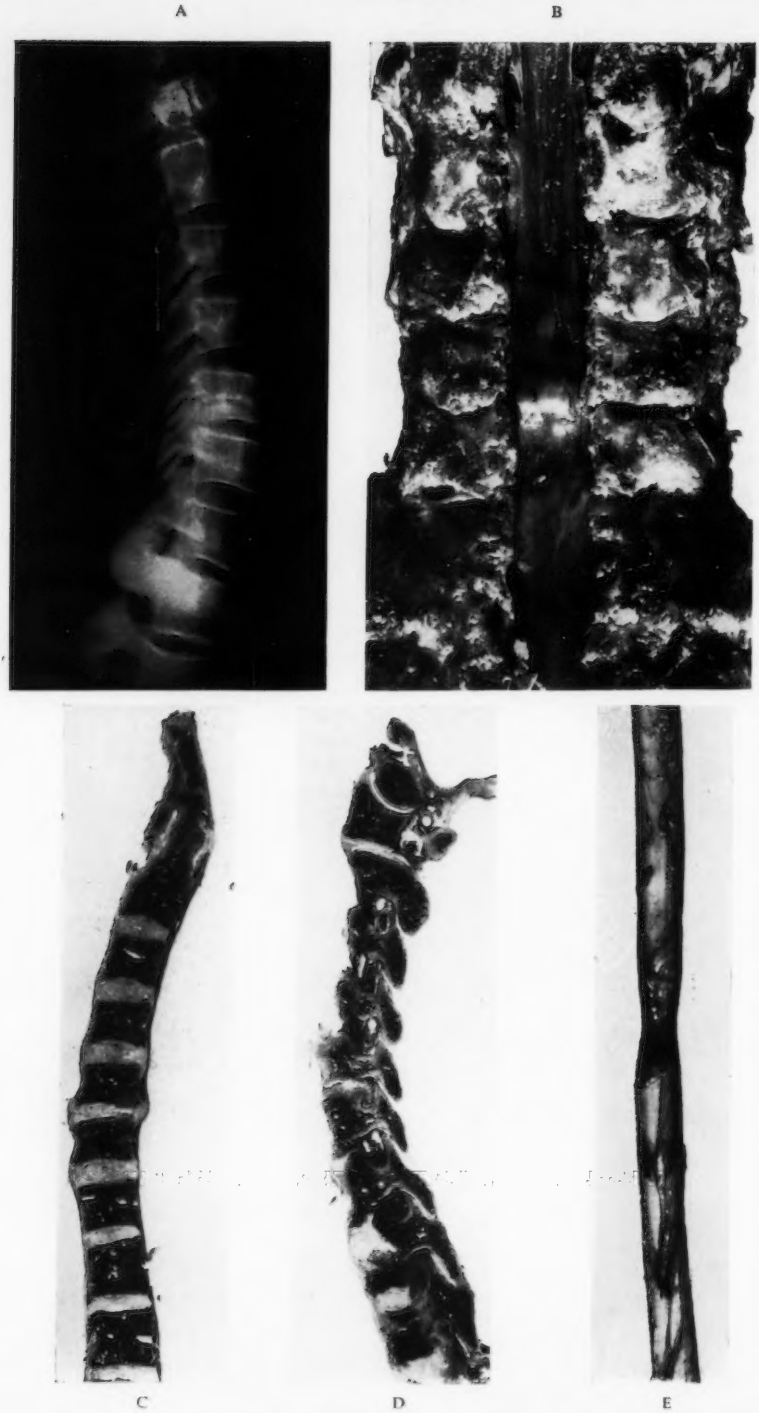
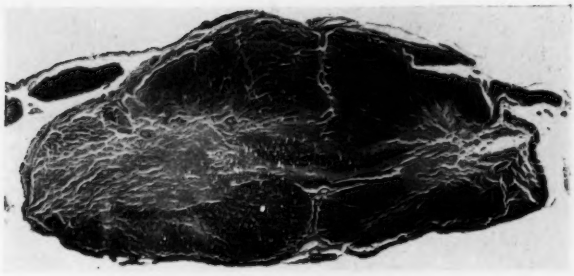


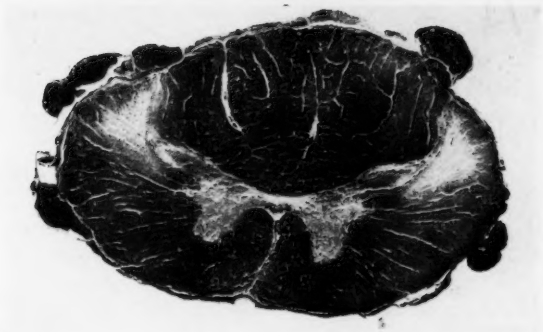
FIG. 15.

To illustrate article by Eric E. Payne and John D. Spillane.

F



G



H

FIG. 15 (*continued*)

To illustrate article by Eric E. Payne and John D. Spillane.

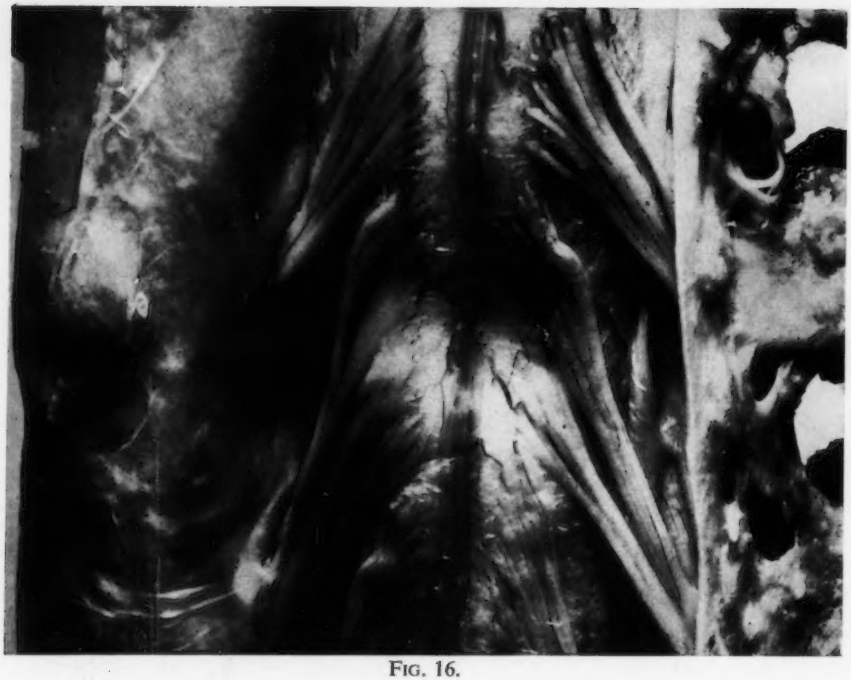


FIG. 16.

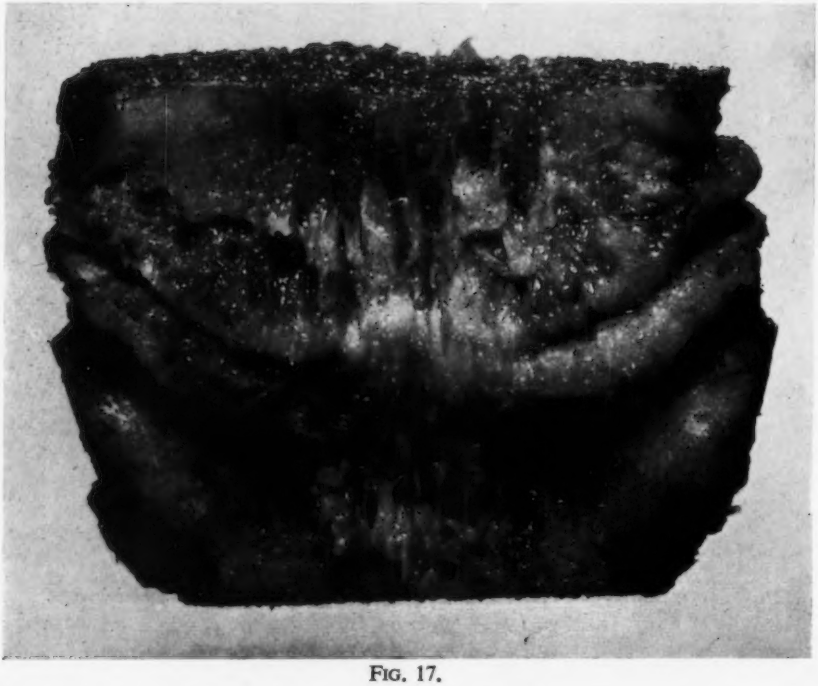
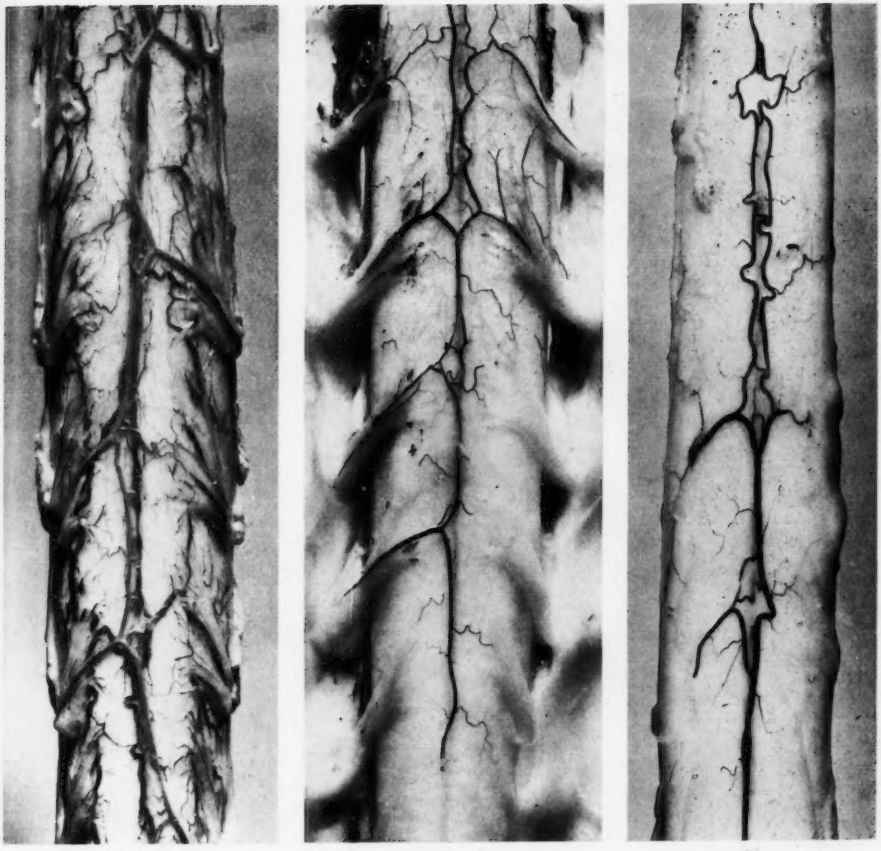


FIG. 17.

To illustrate article by Eric E. Payne and John D. Spillane.

PLATE LXXXI



A B C

FIG. 18.

To illustrate article by Eric E. Payne and John D. Spillane.

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PLATE LXXXII

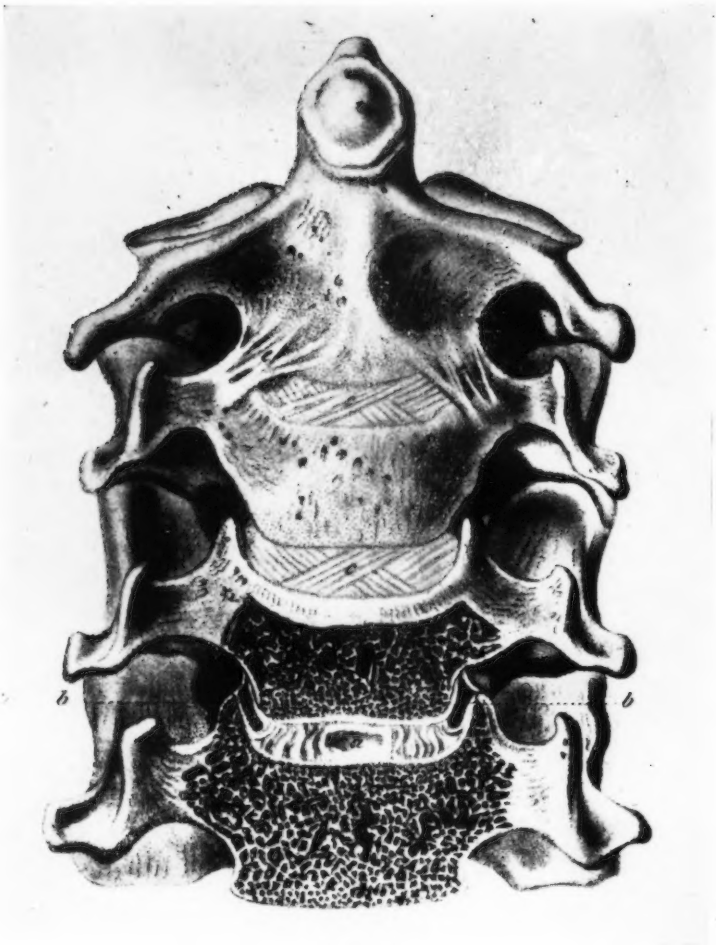

FIG. 19.

To illustrate article by Eric E. Payne and John D. Spillane.

DO THE MOTOR NUCLEI OF THE CRANIAL NERVES RECEIVE CORTICOFUGAL FIBRES? AN EXPERIMENTAL STUDY IN THE CAT

BY

FRED WALBERG

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INTRODUCTION

IN most textbooks of neuroanatomy pyramidal tract fibres are said to pass to the motor nuclei of the cranial nerves. Thus, Krieg (1947) and Mettler (1948), who experimentally have studied corticofugal fibres in more detail, both state in their textbooks that the fibres actually go to the nuclei in question.

On the other hand, Levin (1949), who also has contributed much to our knowledge of the connexions of corticofugal fibres, in a review of the efferent fibres of the precentral region states emphatically that most workers have agreed that the fibres to the tegmentum seem to terminate ventral to the cranial nerve nuclei.

In practically all studies of corticofugal fibres to the motor nuclei of the cranial nerves, the Marchi method has been used. However, this method is not well suited to solve the question whether pyramidal tract fibres virtually terminate in the nuclei under consideration or not, since it does not permit the determination of the ultimate endings of nerve fibres. A perusal of the relevant literature leaves one with the impression that the discrepancies are due to different interpretations of the findings made in Marchi material, since all authors seem to agree that fibres from the pyramidal tract can be followed through the reticular formation towards the motor nuclei of the various cranial nerves.

Positive statements that corticofugal fibres terminate in the motor nuclei of the cranial nerves were given by Muratoff (1893), Weidenhammer (1896), Hoche (1898), Romanow (1898), Piltz (1902), Probst (1903), Mettler (1935*a*, 1935*b*, 1935*c*, 1935*d*, 1947), Hirasawa and Kariya (1936) and Krieg (1954). On the other hand, the existence of such fibres was denied by Boyce (1894), Redlich (1897), Mellus (1899), Kosaka (1904) Lewandowsky (1904), Simpson and Jolly (1907), Poljak (1927), Levin (1936) and Combs (1949), who in Marchi sections of various animals were able to trace fibres from the pyramidal tract to the reticular formation ventral to the motor cranial nerve nuclei only.

XUM

Finally it should be recalled that Ramón y Cajal (1909) in his Golgi material never succeeded in following fibres from the pyramids into the motor nuclei of the cranial nerves, saying: "... il est démontré que les collatérales de la voie pyramidal n'ont pas de connexions directes avec les noyaux moteurs bulbaires" (loc. cit. p. 957), a conclusion also reached by Lorente de Nó (1924).

Since experimental studies with silver impregnation methods do not appear to have been made of this problem, a re-investigation of the question appears justified in order to see whether terminal degeneration occurs in the motor cranial nerve nuclei following lesions of the cerebral cortex or not. This was found to be of interest also because in the spinal cord it has been shown with a modified Bielschowsky method that the pyramidal tract fibres terminate, not on the motor cells, but on intercalated neurons only (Szentágothai-Schimert, 1941). A silver method also is the only way to decide whether fibres passing towards a nucleus, virtually terminate there or not.

Observations and Comments

My attention was directed to this problem when studying corticofugal fibres in three cats originally prepared for other purposes. In all of them (*see* fig. 1), extensive lesions of the cerebral cortex had been made

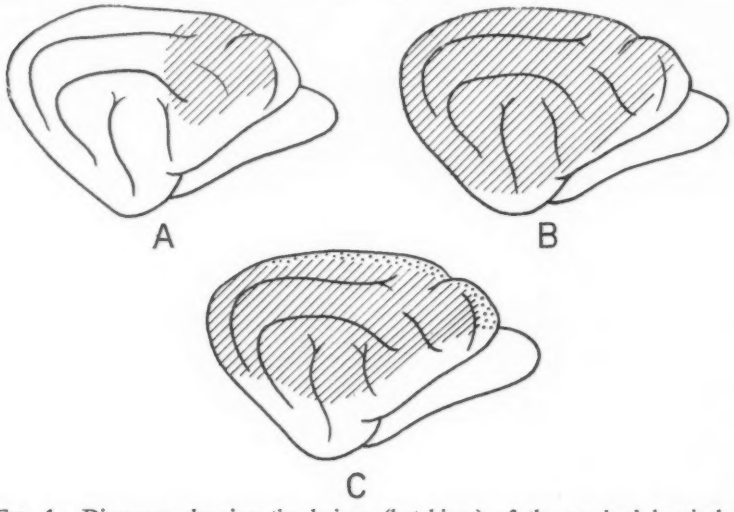

Fig. 1.—Diagrams showing the lesions (hatchings) of the cerebral hemisphere in cats B.St.L. 114 (A), 112 (B) and 113 (C). The dots in figure C indicate areas the fibres from which have been interrupted. Although in these cats various nuclei of the brain-stem show terminal degeneration, no degeneration is present in the motor nuclei of the cranial nerves.

on the right side. In the first cat (B.St.L. 114, killed after twelve days, fig. 1A) only the sensorimotor and adjacent parts of the cerebral cortex were destroyed, in the second (B.St.L. 112, killed after fifteen days, fig. 1B) and the third (B.St.L. 113, killed after seven days, fig. 1C) the cortex was damaged on almost the entire convexity of the hemisphere.[1] Histological control of the lesions shows that in none of the animals the destruction reached the basal ganglia or the thalamus.[2] After perfusion with formalin intravitally and subsequent fixation, the brain-stem was cut in horizontal (cat B.St.L. 112) or in transverse frozen sections (cat B.St.L. 113 and 114) and stained according to Glees' (1946) modification of the Bielschowsky silver method.

Even if in these cats there was abundant terminal degeneration in various nuclei of the brain-stem, e.g. in the pontine nuclei, the inferior olive, the dorsal column nuclei and the nucleus raphe, none of them showed any sign of terminal degeneration in the nuclei of the 3rd, 4th, 6th and 12th nerves, the motor nucleus of the 5th, and the nucleus ambiguus. This means that the termination of the corticofugal fibres, which are supposed to act on the motor nuclei of the cranial nerves, has to be looked for elsewhere, presumably in the reticular formation surrounding these nuclei. No systematic work has been done to locate this termination, but in none of my series did the regions immediately adjacent to the various nuclei show any evidence of terminal degeneration.[3]

It is well known that a localizatory pattern exists in the motor nuclei of the 3rd (Szentágothai, 1942; Warwick, 1953), 5th (Szentágothai, 1949), 7th (Vraa-Jensen, 1942; Szentágothai, 1948), and 12th (J. W. Barnard, 1940, and others) nerves, and in the nucleus ambiguus (Szentágothai, 1943) fibres passing to various muscles of the eye, head, tongue, and larynx, respectively, having their perikarya in different parts of these nuclei. Since it seems far-fetched to assume that fibres from the motor cortex ending diffusely in the brain-stem might convey localized effects to the topically arranged cells in the motor nuclei of the cranial nerves, one might, therefore, expect to find a localization within the termination of corticofugal fibres to the reticular formation. Rossi and Brodal (1956), however, in a recent study of corticoreticular fibres in the cat, found no evidence of such a localization. Regardless of their source within the cortex the fibres were found to terminate in identical parts of the reticular formation. In their study, localized lesions in the motor cortex were not made. It is possible, therefore, that future investigations,

[1]Because of some bleeding in the white matter underneath the lesion, in the latter two cats fibres from the suprasplenial, splenial and cingulate gyri also have been cut.

[2]In cats B.St.L. 112 and 113 the lesions approach the caudate nucleus, without, however, affecting this.

[3]This is of particular interest, since Golgi-studies have shown, that a few dendrites of the cells in the motor nuclei of the cranial nerves penetrate beyond the limits of these nuclei (Cajal, 1909).

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where such discrete destructions are made, may nevertheless reveal that a certain localizatory pattern exists within the termination of cortico-reticular fibres. The recent Golgi-studies of A. B. Scheibel (1955) show that the potential pathways for transmission of impulses in the reticular formation are practically unlimited.

Most reticular neurones sending their axons to the various motor nuclei of the cranial nerves, must be supposed to have very short axons. This is learned from the findings in the various Marchi-studies, in which fibres from the pyramidal tract have been followed to the reticular formation in the neighbourhood of these nuclei. However, some of

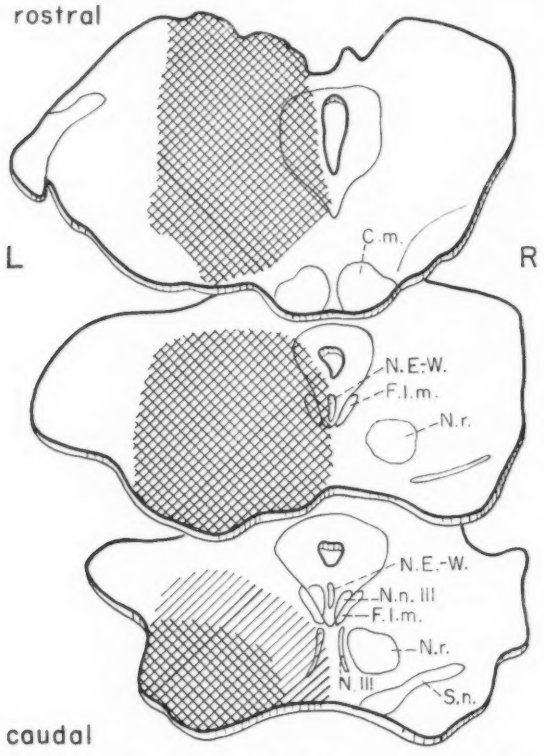

FIG. 2.—Diagrammatic presentation of the lesion in cat B.St.L. 127 with an almost complete hemisection of the mesencephalon on the left side. In this animal some of the motor nuclei of the cranial nerves show terminal degeneration (cp. text). Abbreviations: C.m.: nucleus of the mammillary body. F.l.m.: fasciculus longitudinalis medialis. L: left. N.E.-W.: nucleus of Edinger-Westphal. N.III: 3rd cranial nerve. N.n.III: Nucleus of the 3rd cranial nerve. N.r.: red nucleus. R: right. S.n.: substantia nigra.

the intercalated neurones may also have their perikarya in more remote situations. Thus, in cat B.St.L. 127 (fig. 2, killed ten days after the operation, perfused intravitally), subjected to an almost complete hemisection of the brain-stem on the left side at the level of the oculomotor nucleus, terminal degeneration is present in the facial and trigeminal nuclei on both sides, and in the hypoglossal nucleus on the ipsilateral side. Even if in this animal the lesion includes more than one fibre system and a large area of the brain-stem, the destruction of the reticular formation is so extensive that it might be surmised that part of the terminal degeneration in the motor cranial nerve nuclei is due to damage of cells of this structure, since it is known from Golgi-studies that many cells in the reticular formation send long axons in a caudal direction, some even to the spinal cord, and during their course emit frequent collaterals (M. E. Scheibel, 1955). Such collaterals have been traced to the cranial nerve nuclei. My findings of terminal degeneration in the nuclei of the cranial nerves on the right side, contralateral to the lesion (cat B.St.L. 127, fig. 2), is an indication that axons or collaterals of such intercalated reticular neurones may even cross the mid-line. This is in agreement with observations made in Golgi material.

The findings presented here parallel those made in the spinal cord. Hoff (1932, 1935) and Hoff and Hoff (1934) in their studies with the Cajal method of corticospinal fibres in monkey and cat claim that a few degenerating boutons were found on ventral horn cells. However, later investigations (Phalen and Davenport, 1937; Schimert, 1938; R. I. Barnard, 1940; Szentágothai-Schimert, 1941, and others) have made clear that for judging terminal degeneration in the spinal cord, changes in the boutons are no reliable criteria, since the structure of the boutons may differ considerably in normal preparations. The great variations among normal boutons in the reticular formation have been commented upon by Rossi and Brodal (1956). Furthermore, there may be regional variations even within an apparently uniformly structured nucleus. Thus Blackstad, Brodal and Walberg (1951) in Glees-stained material from the inferior olive in the normal cat found a great proportion of solid boutons in a particular region of the nucleus. Therefore, only when terminal fibres are found in a state of degeneration, should a region containing "degenerating" boutons be considered as showing terminal degeneration.

Employing this criterion, Szentágothai-Schimert (1941) in the cat never found any signs of terminal degeneration on the motor cells of the ventral horns following lesions of the cerebral cortex or the pyramidal tract in the mesencephalon and the medulla. The terminal degeneration was always confined to the cells in the intermediate part of the grey matter of the spinal cord. Lloyd (1941), on the basis of electrophysiological studies in the same animal, likewise concluded that pyramidal

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tract fibres do not establish synaptical contact with the ventral motor horn cells. Recently, however, Bernhard, Bohm and Petersén (1953*a*, 1953*b*), and Bernhard and Bohm (1954*a*, 1954*b*) report electrophysiological findings in the monkey (Macaca mulatta) which they interpret as evidence that in this animal fibres from the pyramidal tract end directly around motor cells of the ventral horns. Such a direct pathway has not been convincingly demonstrated by anatomical methods in monkeys. While it is possible, although not likely, that there may exist species differences with regard to the synaptical connexions of the pyramidal tract fibres in the cord, it is clear that anatomical experiments, in which due regard is taken to changes not only in boutons, but terminal fibres as well, is the only way to settle this question.

My findings also have some bearing on the problem of the tonic innervation of the muscles of the head. The presence in the motor nuclei of the cranial nerves of cells other than those of the large motor type was emphasized by Marinesco (1898) and Ramón y Cajal (1909). Since these cells all show retrograde changes following transection of the facial nerve (Vraa-Jensen, 1942, and others) they cannot be considered as intercalated neurons. However, in the light of the recent findings of an efferent gamma system controlling the tonic activity of the muscle spindle afferents (Leksell, 1945; Hunt and Kuffler, 1951*a*, 1951*b*; Kuffler, Hunt and Quilliam, 1951; for details see also Granit, 1955, pp. 205–210), it seems reasonable to assume that the smaller cells in the motor nuclei of the cranial nerves may belong to this system.

In the literature two routes have been mentioned as possible pathways for the corticofugal fibres to the motor nuclei of the cranial nerves, namely fibres reaching the nuclei directly from the pyramidal tract, and aberrant pyramidal tract fibres descending in the medial lemniscus. These aberrant fibres are said to be distributed mainly to the facial and hypoglossal nuclei.

A certain intermingling of pyramidal tract fibres and fibres of the medial lemniscus at pontine levels was observed by Flechsig (1876). Schlesinger (1896) in human cases of syringomyelia with lemniscal degeneration noted that a bundle of fibres was not degenerated. This bundle joined the fibres of the cerebral peduncle. It was interpreted as the central pathway of the cranial nerves and called the "lateral pontine bundle." A few years later, however, von Bechterew (1899), judging from observations in cases with cortical lesions, produced evidence that the lateral pontine bundle of Schlesinger is a descending tract passing in the medial lemniscus. This observation has subsequently been confirmed and extended by many others. Thus, following lesions of various parts of the cerebral cortex in animals and man, fibres have been described which leave the pyramidal tract and enter the medial lemniscus (Weidenhammer, 1896; Hoche, 1898; Mellus, 1899; Dejerine,

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1901; Sand, 1903; Kosaka, 1904; Simpson and Jolly, 1907; Mettler, 1935*a*, 1935*b*, 1947; Hirasawa and Kariya, 1936; Levin, 1936; Kanki and Ban, 1952; Krieg, 1954; and others). These descriptions have all been based on Marchi material.

Even if, as mentioned, the facial and hypoglossal nuclei are said to be the main terminal areas for these fibres, it is, nevertheless, evident that no one has been able to follow them into the nuclei themselves, the fibres in Marchi-preparations becoming scattered, dwindling at the level of the trapezoid body. In a recent study with the Glees method in the cat (Walberg, 1957) it has, however, been possible to follow these descending degenerating fibres in the medial lemniscus and to establish their area of termination, which was found to be the nuclei of the dorsal columns. In the first part of their course the fibres descend in the pyramidal tract from which they enter the medial lemniscus. Most of these descending fibres in the medial lemniscus which reach the dorsal column nuclei in the cat are very thin. This probably explains why they have not been followed in Marchi material to their ultimate point of destination.

Judging from the findings in the cat it seems reasonable to assume that also in monkey and man corticofugal fibres may reach the nuclei of the dorsal columns via the medial lemniscus, which would explain the findings of previous authors of fibre degeneration in the medial lemniscus following lesions of the cerebral cortex. It appears from my findings that there is no reason to assume that the fibres of the "lateral pontine bundle" end in the motor cranial nerve nuclei.

Though the findings presented in this paper are made on cats, it is likely that also in man the motor nuclei of the cranial nerves receive their impulses from the cerebral cortex via intercalated neurones. Symptoms from the motor cranial nerves accompanying a capsular hemiplegia, therefore, are probably due to interruption of fibres to certain areas of the reticular formation. This should be kept in mind in future studies of pathological human cases.

The findings presented here furnish another example that further studies on the connexions of corticofugal fibres most likely will bring our concept of the function of the pyramidal system into better accordance with clinical observations in man, still poorly understood (for an account on the many problems regarding the anatomy and physiology of the pyramidal tract, *see* Brodal, 1953). For example, the finding of pyramidal tract fibres from the temporal and occipital lobes (Walberg and Brodal, 1953) may explain the presence of so-called pyramidal signs in lesions of the cerebral cortex outside regions considered as the only origin of pyramidal tract fibres. In future investigations of the pyramidal system it is important to use methods which permit the study of details in its anatomical organization.

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SUMMARY

In three cats subjected to extensive cortical ablations, the motor nuclei of the cranial nerves show no signs of terminal degeneration in Glees-stained silver sections. No detailed mapping of terminal degeneration in the reticular formation was undertaken, but it was found that also the region just adjacent to the motor nuclei of the cranial nerves is devoid of corticofugal fibres.

Impulses from the cerebral cortex, therefore, must be assumed to reach these nuclei by way of intercalated neurones lying in the reticular formation. Most of these neurones presumably have short axons, but observations have been made which indicate that some of them may have long axons. Some of the axons of the intercalated neurones probably cross the raphe before they terminate in the motor cranial nerve nuclei.

The anatomical findings made in this study parallel those made in the spinal cord by Szentágothai (1941). The functional significance of the findings is briefly discussed.

REFERENCES

BARNARD, J. W. (1940) *J. comp. Neurol.*, **72,** 489.
BARNARD, R. I. (1940) *J. comp. Neurol.*, **73,** 235.
v. Bechterew, W. (1899) "Die Leitungsbahnen im Gehirn und Rückenmark. Ein Handbuch für das Studium des Aufbaues und der inneren Verbindungen des Nervensystemes." Leipzig.
BERNHARD, C. G., and BOHM, E. (1954*a*) *Arch. Neurol. Psychiat., Chicago,* **72,** 473.
——, —— (1954*b*) *Acta physiol. scand.*, **31,** 104.
——, ——, and PETERSÉN, I. (1953*a*) *Experientia*, **9,** 111.
——, ——, —— (1953*b*) *Acta physiol. scand., Suppl.* **106, 29,** 79.
BLACKSTAD, T., BRODAL, A., and WALBERG, F. (1951) *Acta anat.*, **11,** 461.
BOYCE, R. (1894) *Proc. roy. Soc.*, **56,** 305.
BRODAL, A. (1953) *Irish J. med. Sci.*, p. 289.
COMBS, C. M. (1949) *J. comp. Neurol.*, **90,** 373.
DÉJERINE, J. (1901) "Anatomie des centres nerveux." Paris, vol. II.
FLECHSIG, P. (1876) "Die Leitungsbahnen im Gehirn und Rückenmark des Menschen auf Grund entwicklungsgeschichtlicher Untersuchungen dargestellt." Leipzig.
GLEES, P. (1946) *J. Neuropath.*, **5,** 54.
GRANIT, R. (1955) "Receptors and sensory perception. A discussion of aims, means, and results of electrophysiological research into the process of reception." New Haven.
HIRASAWA, K., and KARIYA, K. (1936) *Okajimas Folia anat. jap.*, **14,** 603.
HOCHE, A. (1898) *Arch. Psychiat. Nervenkr.*, **30,** 103.
HOFF, E. C. (1932) *Proc. roy. Soc., B,* **111,** 226.
—— (1935) *Arch. Neurol. Psychiat., Chicago,* **33,** 687.
——, and HOFF, H. E. (1934) *Brain*, **57,** 454.
HUNT, C. C., and KUFFLER, S. W. (1951*a*) *J. Physiol.*, **113,** 283.
—— (1951*b*) *J. Physiol.*, **113,** 298.
KANKI, S., and BAN, T. (1952) *Med. J. Osaka Univ.*, **3,** 201.

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KOSAKA, K. (1904) *Mitt. med. Fak., Tokio*, **5**, 77.
KRIEG, W. J. S. (1947) "Functional Neuroanatomy." Philadelphia.
—— (1954) "Connections of the Frontal Cortex of the Monkey." Springfield, Ill.
KUFFLER, S. W., HUNT, C. C., and QUILLIAM, J. P. (1951) *J. Neurophysiol.*, **14**, 29.
LEKSELL, L. (1945) *Acta physiol. scand., Suppl.* **31.**
LEVIN, P. M. (1936) *J. comp. Neurol.*, **63**, 369.
—— (1949) "Efferent Fibers." *In* Bucy, P. C. "The precentral motor cortex." 2nd edition. Urbana, Ill.
LEWANDOWSKY, M. (1904) *Denkschr. med.-naturw. Ges. Jena*, **10**, 63.
LLOYD, D. P. C. (1941) *J. Neurophysiol.*, **4**, 525.
LORENTE DE NÓ, R. (1924) *Trab. Lab. Invest. biol. Univ. Madr.*, **22**, 51.
MARINESCO, G. (1898) *Rev. neurol.*, **6**, 30.
MELLUS, E. L. (1899) *J. nerv. ment. Dis.*, **26**, 197.
METTLER, F. A. (1935*a*) *J. comp. Neurol.*, **61**, 221.
—— (1935*b*) *J. comp. Neurol.*, **61**, 509.
—— (1935*c*) *J. comp. Neurol.*, **62**, 263.
—— (1935*d*) *J. comp. Neurol.*, **63**, 25.
—— (1947) *J. comp. Neurol.*, **86**, 119.
—— (1948) "Neuroanatomy." 2nd edition. St. Louis.
MURATOFF, W. (1893) *Arch. Anat. Physiol.* (*Anat. Abt.*), 97.
PHALEN, G. S., and DAVENPORT, H. A. (1937) *J. comp. Neurol.*, **68**, 67.
PILTZ, J. (1902) *Neurol. Zbl.*, **21**, 482.
POLJAK, S. (1927) *J. comp. Neurol.*, **44**, 197.
PROBST, M. (1903) *Jb. Psychiat. Neurol.*, **23**, 18.
REDLICH, E. (1897) *Neurol. Zbl.*, **16**, 818.
RAMON Y CAJAL, S. (1909) "Histologie du système nerveux de l'homme et des vertébrés." Paris, vol. I.
ROMANOW, M. P. (1898) *Neurol. Zbl.*, **17**, 593.
ROSSI, G. F., and BRODAL, A. (1956) *J. Anat., Lond.*, **90**, 42.
SAND, R. (1903) *Arb. neurol. Inst. Univ. Wien.*, **10**, 185.
SCHEIBEL, A. B. (1955) *Anat. Rec.*, **121**, 361.
SCHEIBEL, M. E. (1955) *Anat. Rec.*, **121**, 362.
SCHIMERT, J. (1938) *Z. Anat. EntwGesch.*, **108**, 761.
SCHLESINGER, H. (1896) *Neurol. Zbl.*, **15**, 146.
SIMPSON, S., and JOLLY, W. A. (1907) *Proc. roy. Soc. Edinb.*, **27**, 281.
SZENTÁGOTHAI, J. (1942) *Arch. Psychiat. Nervenkr.*, **115**, 127.
—— (1943) *Z. Anat. EntwGesch.*, **112**, 704.
—— (1948) *J. comp. Neurol.*, **88**, 207.
—— (1949) *J. comp. Neurol.*, **90**, 111.
SZENTÁGOTHAI-SCHIMERT, J. (1941) *Z. Anat. EntwGesch.*, **111**, 322.
VRAA-JENSEN, G. (1942) "The Motor Nucleus of the Facial Nerve. With a Survey of the Efferent Innervation of the Facial Muscles." Copenhagen.
WALBERG, F. (1957) *Brain*, **80**, 273.
——, and BRODAL, A. (1953) *Brain*, **76**, 491.
WARWICK, R. (1953) *J. comp. Neurol.*, **98**, 449.
WEIDENHAMMER, W. (1896) *Neurol. Zbl.*, **15**, 191.

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TERMINATION OF THE CENTRAL PAIN PATHWAY IN MAN: THE CONSCIOUS APPRECIATION OF PAIN

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INTRODUCTION

PAIN is perhaps the most fundamental modality of sensation in animals, and probably phylogenetically the oldest sensory system. For this very reason, its organization in the central nervous system may be expected to be complicated, and to a large extent masked by more recently developed afferent systems.

An ascending fibre system in the anterolateral quadrant of the spinal cord was described by Gowers (1878). Edinger (1889) demonstrated that this tract contained crossed fibres from the contralateral posterior horn of the spinal cord, and Quensel (1898) showed that such fibres in man terminate in the posteroventral part of the thalamus. Spiller (1905) was the first to prove conclusively that this pathway mediates sensations of pain and temperature.

Mott (1895) traced fibres from Gowers' tract up as far as the thalamus in monkeys, but Wallenberg (1899) in the rabbit, and van Gehuchten (1901) in the rabbit and the dog, were unable to trace ascending degeneration rostral to the mesencephalon by the Marchi technique. Glees (1953) stressed that only in primates do myelinated fibres of Edinger's tract reach the thalamus. Mehler (1957) has examined this tract in a series of mammalia by the silver impregnation method of Nauta and Gygax (1954). He finds that very few fibres reach the thalamus in marsupials (approximately 2 per cent), while in primates many more fibres from the anterolateral column of the cord terminate in the specific sensory nucleus of the thalamus (approximately 20 per cent in the monkey and 30 per cent in the chimpanzee). Thus it may be assumed that the direct spinothalamic pathway is phylogenetically recent, as is the case with other long ascending and descending tracts.

As lower animals undoubtedly react strongly to painful stimuli, this sensation must be mediated through sub-diencephalic way-stations. That fibres from the anterolateral funiculus of the cord in man terminate in sub-diencephalic centres is evidenced by the fact that many observers

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(Collier and Buzzard, 1903; Walker, 1943; Gardner and Cuneo, 1945; Morin, Schwartz and O'Leary, 1951; and Glees, 1953) have noted the paucity of fibres entering the thalamus compared with the large bundles found in the anterolateral quadrant of the spinal cord.

A spino-tectal element both crossed and uncrossed, has long been recognized, and is described by von Sölder (1897), Bruce (1898), Russell (1898), Wallenberg (1899), Stewart (1901), Thiele and Horsley (1901) and Walker (1940). Another relay nucleus with which Edinger's tract has connexions is the lateral reticular nucleus of the medulla oblongata, shown by Brodal (1943) to project to the cerebellum. Termination in this nucleus has been noted by Tooth (1892), Wallenberg (1899), Kohnstamm (1900), Petrén (1901), Collier and Buzzard (1903), May (1906) and Brodal (1949).

The medullary reticular formation has been implicated as a site of termination for these fibres by some early authors, though in the last forty years little has been written of such connexions. The medullary reticular formation was very accurately described, together with its afferent and efferent connexions by Kohnstamm and Quensel (1908), who also gave their views on the function of the system, which they regarded as a "centrum receptorium," and these are remarkably close to modern concepts. These authors stated that fibres of Edinger's tract end bilaterally in the medullary reticular formation. Other early authors (Bruce, 1898; Collier and Buzzard, 1903; May 1906 and Petrén, 1910) who observed termination at this level do not state clearly whether such endings were unilateral or bilateral.

Some authors have also observed terminal degeneration of this tract at more rostral levels of the brain-stem reticular formation, including Wallenberg (1899), Kohnstamm (1900), May (1906), Petrén (1910) and Walker (1940). Morin and O'Leary (1950) had noted termination in the medullary reticular formation, using electrophysiological techniques, but in an anatomical elaboration of this work (Morin, Schwartz and O'Leary, 1951) stated that they saw little degeneration in the reticular formation rostral to the olive.

With the exception of Brodal (1949), who was interested only in the lateral reticular nucleus and Glees and Bailey (1951), all the authors cited had used the Marchi technique, which of course stains only degenerating medullary sheaths. It is apparent from the careful study of Häggqvist (1936) that the majority of fibres in the anterolateral funiculi of the spinal cord do not possess a myelin sheath of the classical type, and therefore cannot be stained by this method. This point is emphasized by White and Sweet (1955, p. 46) who state that from surgical experience "it is evident that the pain pathways are by no means co-extensive with those shown by Marchi degeneration."

It has thus been felt worth while to undertake an investigation of

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axon degeneration by modern silver impregnation techniques of human material following anterolateral cordotomy or medullary tractotomy. A parallel investigation in monkeys has been made by Mehler, Feferman and Nauta (1956), and by Johnson (1954) in cats; both of these have been published in abstract. Very recently, Rossi and Brodal (1957) have published their observations on the termination of spino-reticular fibres in the cat. These investigations, like the present one, have been made by silver methods, and the results are set out in comparison with those of the present author in Table II.

Materials and Methods

The brains of 4 subjects, dying between 14 and 50 days after tractotomy for the relief of persistent pain were used in this investigation. 3 of the patients had unilateral operations, one bilateral; in this latter case, it was felt that there would be significant axonal changes resulting from both operative interventions. In all the patients, there was a satisfactory level of analgesia and thermanæsthesia subsequent to operation, and this was maintained up to the time of death. In no case was there any sign of pyramidal tract damage, or of damage to any other modality of sensation except pain and temperature which could be observed on careful clinical testing.

The brains were removed from the subjects within twelve hours of death and immersed in 10 per cent formalin. This was changed after three months and blocks were cut five or six months after the beginning of the fixing process.

In all cases, the whole diencephalon and brain-stem were cut in serial section. 3 of these (Cases 1, 3 and 4) were cut in frozen section at 30 μ, with an interval of 300 μ between sections, by a modification of the method of Marshall (1940); these were impregnated by the method of Nauta (Nauta and Gygax, 1954), using Laidlaw's ammoniacal silver solution. The remaining brain-stem and diencephalon (Case 2) was

Table I

Case No.	*Surgeon*	*Operation*	*Time of death: days after operation*	*Method of examination*
1	Dr. W. H. Sweet	Left medullary tractotomy	14	Nauta
2	Sir Geoffrey Jefferson	Right thoracic tractotomy	28	Glees
3	Mr. A. Sutcliffe Kerr	Left cervical tractotomy	24	Nauta
		Right thoracic tractotomy	50	
4	Mr. A. Sutcliffe Kerr	Right thoracic tractotomy	17	Nauta

embedded in celloidin, cut at 15 μ with an interval of 300 μ between sections and impregnated by the method of Glees (1946). As controls, sections from serially cut normal brain-stems obtained and fixed in the same manner were impregnated by both techniques. Further control was achieved by noting the absence of degenerating axons in closely related nuclei in the same sections as those in which degeneration was observed. These are illustrated in figs. 2, 4, 6 and 8. Details of the cases and staining methods are set out in Table I.

Observations

Recent silver techniques which claim to demonstrate axonal degeneration have been subject to considerable criticism on the grounds that artefact may mimic true degeneration to such an extent as to make differentiation impossible. In order to meet such criticisms, two factors must be discussed, (*a*) the criteria of true degeneration as seen with these impregnations, and (*b*) the recognition and causes of artefact.

(*a*) *Criteria of Axonal Degeneration*

When the Glees technique was originally introduced (Glees, 1946) it was thought to demonstrate degeneration of the bouton terminal. Recently, however, Weber (1955) has shown that the normal boutons terminaux undergo cyclical phases of degeneration and regeneration. As these changes are out of phase with one another for a large number of boutons, normal material should show only a small number of degenerating boutons terminaux at any given moment in time. Thus it may be argued that if a large number of boutons terminaux are seen to be in a degenerative phase at the same time in any given area, true degeneration of the parent neurons may be inferred. However, Brodal, who has probably the largest experience with this technique, has recently rejected the interpretation of any appearance of the bouton terminal as being diagnostic of degeneration of the neurone (Rossi and Brodal, 1956). The large number of forms described by Brodal appear to correspond fairly closely to the forms described in the cyclical changes of Weber (1955). Thus it is safer not to accept any appearance of the bouton terminal as being diagnostic of neuronal degeneration.

The appearance of the degenerating preterminal neurons, i.e. terminal axon or telodendria, has been discussed by Glees and Nauta (1955). These authors stress the droplet nature of the deposited silver on a degenerating nerve fibre. Two criteria must be satisfied before true degeneration can be inferred: complete discontinuity between the droplets, and an orderly arrangement of the droplets. With regard to the latter criterion, straight lines of droplets are interpreted as being fibres *en passage*, while spiral or curved forms in close proximity to nerve cells are taken as being preterminal fibres.

Finally, two further safeguards may be employed in the use of these methods. Degeneration should not be assumed where only one, or a very few, degenerating fibres can be seen; and, if possible, the observations should be checked against those obtained with well-tried non-silver techniques (e.g. Marchi). The results described in the present paper have mostly been demonstrated by earlier authors with the Marchi technique; but the use of silver methods allows a far greater accuracy of definition with regard to precise nuclear terminations.

(*b*) *The Recognition and Causes of Artefact*

It is well known that silver degeneration methods will only "take" if death has occurred within a restricted period following the production of the lesion. Evans and Hamlyn (1956) have undertaken an investigation of the time sequence of the two techniques employed by the present author. They state that Nauta degeneration can be seen as early as three days after the lesion in rabbits, and is fully established by five days. In primates, however, the period appears to be longer. Glees and Nauta (1955) did not see satisfactory Glees degeneration in the monkey before seven days. Meyer (1949) has also seen Glees degeneration in the human brain at seven days.

At the other end of the scale, Evans and Hamlyn (1956) have observed maximal Nauta degeneration in the rabbit up to 45 days after the lesion, and they further state that some degenerating material persists up to 112 days in this animal. No observations are available on the latest time at which degeneration can be seen in Glees material in mammals. Meyer's (1949) longest time interval in human cases was 20 days; Evans and Hamlyn (1956) state that most Glees material has disappeared from the avian optic tectum by 28 days, while Armstrong (1950) observed that most of this material has disappeared from the reptilian optic tract in 25 days, though some persists up to 70 days.

The fact that the time sequence is different for the two silver methods under discussion, and that the Glees technique will impregnate alcohol-treated material, while the Nauta method fails to do so, indicates, as Evans and Hamlyn (1956) have stated, that different components of the axoplasm must be revealed by the two methods. Thus it is valuable, as in the present observations, to find that the two techniques check each other.

Proper fixation is probably the most important factor in the avoidance of artefact by the use of these techniques. Ideally, fixation should be achieved at the time of death by intra-arterial perfusion of formalin; this is obviously impossible with human material. The question therefore arises as to whether, and to what extent, post-mortem degeneration occurs in previously normal neurones which is revealed by impregnation by these methods. With the Glees technique, Meyer (1949) achieved satisfactory results from ordinary post-mortem material. The present

author is, so far as he knows, the first to apply the Nauta technique to human post-mortem material. Brains from human subjects who had not been subjected to recent neurosurgical interference were fixed, sectioned and stained in the same manner as the material under investigation. No appearances suggestive of degeneration were seen, although if the permanganate stage of the technique were shortened, a large number of normal fibres are impregnated. An investigation is currently in progress with animal material to establish the time limits within which it is safe to presume that post-mortem degenerative changes do not occur with these techniques.

Adequate, and even prolonged fixation, is necessary to avoid many of the true artefacts, as opposed to post-mortem degeneration described below. There is little doubt, also, in the view of the present author, that delay in the period between death and fixation is a fruitful source of true artefact. Nauta (1955) stresses that fixation for primate material, using his technique, should be for four to six months. He finds, moreover, that artefact can be reduced by acidification of the fixative, (10 per cent formalin) with 1 per cent formic acid for twenty-four hours before the blocks are cut.

Artefact may also be reduced, as is well known, by the use of scrupulously clean glassware, fresh and filtered solutions for staining, prolonged washing in several baths of distilled water after the impregnation is completed: rinsing through sodium thiosulphate is also useful at this stage.

Artefacts arise in both methods by the deposition of excess metallic silver; in the Nauta technique, they also arise from the deposition of manganese dioxide (MnO_2), which has a black granular appearance identical to that of reduced silver plan when seen under the microscope.

Excessive deposition may occur either on the neuron, or generally. In the first case, this can give rise to a varicose appearance of the axoplasm. Glees (1948) has argued that this can be caused by very early degeneration of the axon; but the majority of authors, including the present writer, prefer to reject this appearance, when unaccompanied by true droplet degeneration, as an artefact. The present author has noted that when these varicosities of the axon are abundant, there is often an excessive deposition of silver on other parts of the neurone. Thus, the cells, instead of being a rich tobacco-brown colour, are black and granular, and the dendrites are also impregnated. While this appearance of the cell (but not of the dendrite) is normal for pigmented nuclei, such as the substantia nigra and the locus cœruleus, in general it forms a useful criterion for the rejection of unsatisfactorily impregnated sections.

The second type of artefact consists in the generalized deposition of reduced silver (and/or MnO_2 in the case of the Nauta technique). This constitutes a far more serious hazard than over-deposition on the neuron,

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though the two types frequently occur together. Unless the strictest standards are exercised, it is easy to mistake this appearance for true terminal degeneration, especially when it occurs patchily and in nuclear areas where one might perhaps expect to see true degeneration. Sometimes, of course, it occurs in addition to true degeneration; unless the latter is very well marked, it is better to reject such sections. This general deposition is characterized by its lack of orderly arrangement (*see* fig. 4), while in true degeneration, the outline of fibre pattern can always be seen.

The classification of thalamic nuclei used is that of Dekaban (1953), while the nuclei of the sub-diencephalic brain-stem are described according to the atlas of Olszewski and Baxter (1954).

A large amount of degeneration was seen in the ipsilateral specific sensory nucleus of the thalamus (n. ventralis postero-lateralis) (fig. 1). This was much more easily seen in the Nauta-impregnated sections as in the Glees sections there was a very heavy overlay of normal fibres. This finding is in conformity with that of a very large number of observers, of whom the earliest was Henneberg (1901). A little degeneration was also seen in the contralateral specific thalamic nucleus an observation that had previously been made by Walker (1938), and confirmed by Chang and Ruch (1947).

It has long been recognized that the spinothalamic bundle passes through the centre médian *en route* for the ventroposterior nucleus, but previous workers have not described termination in this nucleus, as has been demonstrated ipsilaterally in the Nauta material of the present series (fig. 3). However, Le Gros Clark (1936) and Mehler, Feferman and Nauta (1956), working with the macaque, have observed degeneration in closely related intralaminar nuclei, particularly n. centralis lateralis. N. centrum medianum is relatively larger in man than in the lower primates, and may perhaps take over some of the connexions of n. centralis lateralis.

A few scattered fibres, apparently degenerating, were seen in the ipsilateral thalamic reticular nucleus in a few sections. This appearance has also been observed recently in Glees material by Getz (1952) in cats, but Mehler, Feferman and Nauta (1956) failed to find any degeneration in this nucleus in macaques after careful searching.

Fibres destined for the contralateral thalamus reach it by way of the dorsal part of the posterior commissure. Degenerating fibres of passage in this location, following damage to the antero-lateral quadrant of the spinal cord, have been recorded by Quensel (1898), Wallenberg (1899) and Chang and Ruch (1947), employing the Marchi technique.

In confirmation of the findings of many earlier investigators, terminal

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degeneration was found in the superior and inferior colliculi and ipsilaterally in the so-called "lateral reticular nucleus" of the medulla which relays to the cerebellum.

Among the brain-stem reticular nuclei of unknown connexions, extensive degeneration was found bilaterally in the medial reticular formation (figs. 5 and 7). More fibres and nuclear groups were involved in the medulla oblongata and the giganto-cellular complex (fig. 7) than in the more rostral parts of the brain stem; in the pons only 3 nuclei were involved, while in the mesencephalon degeneration was found in 4 tegmental nuclear groups in addition to the colliculi (fig. 5). A list of nuclei in which degeneration was found is given in Table II, and compared with the findings of Johnson (1954), Mehler, Feferman and Nauta (1956) and Rossi and Brodal (1957). The findings in the present investigation are in agreement with all the other authors in that the greatest amount of terminal degeneration is found at medullary level, in the nucleus medullæ oblongatæ centralis and the caudal part of the nucleus giganto-cellularis; that degenerating terminals in the lateral part of the medullary reticular formation (n. parvocellularis) are extremely sparse; and that terminal degeneration is found in the central pontine nuclei.

Johnson (1954) and Rossi and Brodal (1957) do not appear to have examined the mesencephalic tegmentum for spino-reticular degeneration. Although such degeneration was seen by the present author in 4 nuclei, it was quantitatively small in amount.

The question of lateralisation produces some disagreement. Mehler, Feferman and Nauta (1956) do not commit themselves on this matter; Johnson (1956) says that these systems are "principally homolateral." Rossi and Brodal (1957) state that "there is a preponderance of homolateral terminations, particularly in the medullary reticular formation . . . (but) . . . at the pontine level the fibres are distributed more equally to both sides." On the other hand, their illustration of the distribution of terminal degeneration in cat Sp.C.L.26 appears to show almost as much contralateral as ipsilateral degeneration in the medulla. Glees (1952), describing Marchi studies in monkeys, saw fibres ending in the medial medullary reticular formation of both sides from unilateral cordotomies. In the present study the difference in amount of degeneration did not appear very striking between the two sides, even at medullary level.

Degenerating fibres of passage could be seen in the medulla, together with fibres turning medially and crossing to the other side.

There was no very apparent difference in the amount of degenerating material seen between the case which had been operated on bilaterally (Case 3) and the other 3 cases; but it must be remembered that the Nauta technique in particular is of very little quantitative value. There was

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a very close correspondence between the findings in the two impregnation techniques employed.

Text-fig. 1 is a schematic diagram of the termination of the central pain pathway as seen by the present author.

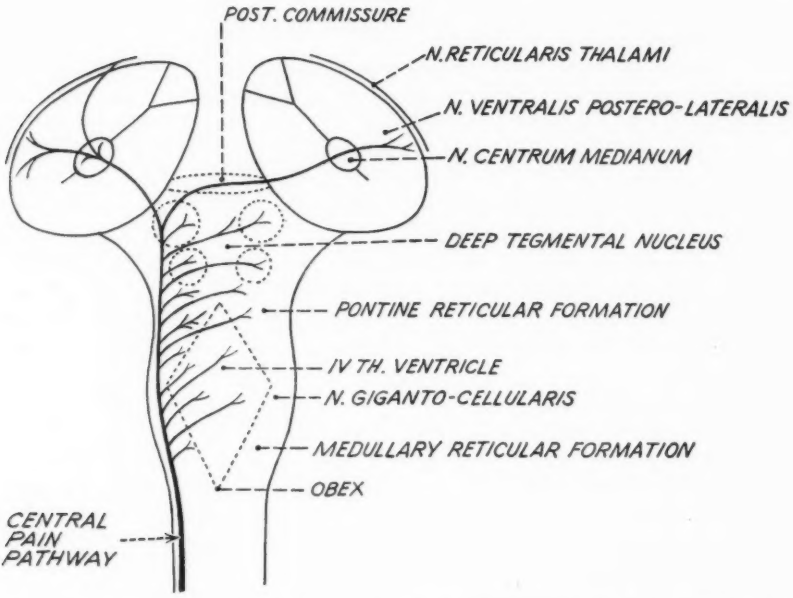
TABLE II.—NUCLEI OF BRAIN STEM RETICULAR FORMATION RECEIVING AFFERENT FIBRES FROM THE ANTEROLATERAL FUNICULUS OF THE SPINAL CORD

Author	*Johnson*, 1954	*Rossi and Brodal*, 1957	*Mehler Feferman and Nauta*, 1956	*Bowsher*
Method	*Nauta*	*Glees*	*Nauta*	*Nauta and Glees*
Animal Studied	*Cat*	*Cat*	*Macaque*	*Man*
Nucleus				
Periaqueductal Grey Matter	+		+	+
N. intercollicularis			+	
N. interstitialis (Cajal)				+
N. paralemniscalis				+
N. tegmenti pedunculopontinus (Kölliker)				+
Griseum centrale pontis			+	+
Nn. pontis oralis et caudalis	+	+	+	+
N. subcoeruleus		+	+	+
N. gigantocellularis	+	+	+	+
Nn. paragigantocellularis dorsalis et lateralis	+	+	+	+
N. parvocellularis	+	+	+	+
N. medulæ oblongatæ centralis	+	+	+	+
N. raphæ pallidus			+	+
N. interfascicularis hypoglossæ			+	
N. subtrigeminalis			+	

This Table does not include brain stem nuclei of known connections (i.3. cranial nerve and relay nuclei) shown to receive afferents from the cord.

DISCUSSION

The direct spino-thalamic pathway, which is said to contain only 1,500 medullated fibres at the level of the superior colliculus (Glees and Bailey, 1951), terminates in the thalamic nucleus ventralis postero-lateralis, in common with the medial lemniscus. Thus this nucleus is believed to receive all fibres mediating conscious somatic sensation below the area of distribution of the fifth cranial nerve. Its somatotopical projection to the sensory cortex is well recognized, though some doubt has been expressed as to whether pain sensation is cortically represented, some holding that it is consciously appreciated at thalamic level. However, in view of the very small number of pain fibres reaching the specific thalamic nucleus in comparison with the very large number of fibres from the medial lemniscus, one would expect the cortical representation



TEXT-FIG. 1.—Diagrammatic representation of the termination of the central pain pathway, as revealed in the present investigation.

of pain, if it exists, to be very small. In fact, out of 426 sensory responses recorded in conscious patients as the result of cortical stimulation by Penfield and Boldrey (1937), 11 (2·5 per cent) were described as painful. Such a percentage appears to accord with the limits imposed by the relative numbers of fibres reaching the thalamus and subserving different sensory modalities. Moreover, the type of pain evoked was sharp and well localized.

The description of conscious sensation is a purely subjective matter, and thus open to differing interpretation in each individual. Man is the only animal capable of describing his sensory experiences, so that interpretation of sensory modalities in lower animals with a similar anatomical organization is at best only possible by analogy with man.

In everyday subjective experience, there are two quite different conscious sensations which are described as "pain." In the normal individual, these two sensations are always temporally associated, which is probably why the same word is used to describe both. The first is a sharp well-localized sensation which persists contemporaneously with the evoking stimulus; though if this latter is applied for a long time, the mechanism may show attenuation or fatigue. It is known that this

first type of painful sensation, together with other modalities of conscious sensation, disappears if the specific sensory nucleus of the thalamus is destroyed (Dejerine and Roussy, 1906). It may therefore be assumed that this type of pain is mediated by the direct spinothalamic fibres which reach the nucleus ventralis postero-lateralis. The fact that these direct fibres to the specific sensory nucleus are found in both thalami is only further evidence of the greater bilaterality of conscious representation which is now being recognized (Penfield and Jasper, 1954).

The second type of sensation commonly described as "painful" is a diffuse, poorly localized, feeling with an appreciably longer perception interval between provoking stimulus and consciousness, and which persists in time beyond the withdrawal of the initiating stimulus. In the thalamic syndrome of Dejerine and Roussy (1906), this is the only type of pain which is felt.

Some authors (Gasser, 1934, 1943) have attempted to explain these two types of pain by the difference in rate of conduction of peripheral pain fibres, following the demonstration by Zotterman (1933) of fast- and slowly-conducting peripheral pain fibres. While this theory may well explain in whole or in part, the difference in conduction time and temporal persistence of the two sensations, their dissociation in cases of thalamic syndrome argues a difference in central organization, at least in so far as their conscious representation is concerned. Several authors (May, 1906, Petrén, 1910, Lashley, 1954) have predicated a second central pain pathway made up of short chains of internuncial neurones, on the basis of the anatomical connexions of fibres from the anterolateral funiculus of the cord.

In attempting to explain the anatomical substrate of diffuse pain, the further connexions of the brain-stem nuclei, in which so much terminal degeneration of fibres from the anterolateral funiculus of the cord is found, are important. Termination in the lateral reticular nucleus of direct or collateral exteroceptive fibres (Brodal, 1943) is now well known and requires no further discussion from the point of view of the present paper.

The spino-tectal element in this quadrant of the cord has also long been recognized, and Walker (1943) suggests that it is an integral part of the central pain pathway. Rioch (1929) and Bucher and Bürgi (1945) have demonstrated that cells in the tectal and pretectal regions project to the centromedian and parafascicular nuclei of the thalamus.

The reticular elements of the brain-stem tegmentum, which according to Hines (1955) are relatively larger in man than in lower animals, show quantitatively the greatest amount of degeneration from the afferent fibres in question. As early as 1908, Kohnstamm and Quensel postulated the existence of a reticulo-thalamic tract. Russell (1954) has suggested that this is the "dorsal trigemino-thalamic tract" of Wallenberg (1901).

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This hypothesis is supported by Bürgi (1955), and was previously suggested by Lewandowsky (1904). Magoun and McKinley (1942) demonstrated that thalamic potentials evoked by peripheral nerve stimulation appear not only in the ventro-posterior nucleus, but after some delay, in the centre médian; French, Verzeano and Magoun (1953) found that in the monkey, stimulation of the brain-stem reticular formation caused the appearance of evoked potentials in the centre médian and other intralaminar nuclei of the thalamus, while Johnson (1953) showed, with the Nauta technique in the cat, that these thalamic nuclei receive afferent fibres from the periaqueductal grey and deep tegmental nucleus in the cat. Magoun (1952) has traced this pathway by electrophysiological techniques.

Thus it would appear, from the weight of experimental evidence, that reticular nuclei of the lower brain-stem project to the centro-median and other intralaminar nuclei of the thalamus. While it is possible that some fibres reach it direct from the anterolateral funiculus of the cord, it is certain that others reach it over axons of varying length, and therefore with varying numbers of interposed synapses. Papez (1956) has recently reviewed the afferent pathways from the reticular formation to the intralaminar thalamic nuclei, and describes the bulbo-thalamic and tegmento-thalamic tracts as being the chief routes concerned.

These intralaminar nuclei are known to be the starting point of the diffuse thalamo-cortical projection system first described by Morison and Dempsey (1942). How such impulses from the thalamic recruiting nuclei finally reach the cortex is still a matter of considerable controversy, but this is outside the scope of the present paper. For the purposes of the present argument, the connexions of the central pain pathway are schematically summarized in text-fig. 2.

The diffuse spino-reticulo-thalamo-cortical system is ideally organized for the mediation of diffuse, poorly localized pain. Its multi-neuronal pathway would account for the delay in conduction; its multi-synaptic connexions would account for persistence of cortical bombardment after the withdrawal of the provoking stimulus; and its diffuse cortical projections may account for its poor localization. It persists after the destruction of the specific thalamic nucleus in classical thalamic syndrome; conversely, Hécaen *et al.* (1949) have shown that in this condition, electro-coagulation of the centre médian abolishes the diffuse pain. Morison, Finley and Lothrop (1943) call this nucleus the "master oscillator" of the diffuse projection system. Starzl and Whitlock (1952) observed that in a primate (*Macaca mulatta*) the greater part of the diffuse thalamocortical projection goes to the frontal association areas, while Hanbery, Ajmone-Marsan and Dilworth (1943) have demonstrated that stimulation of the medial part of the brain-stem reticular formation—the part in which terminal degeneration has been noted above—gives the

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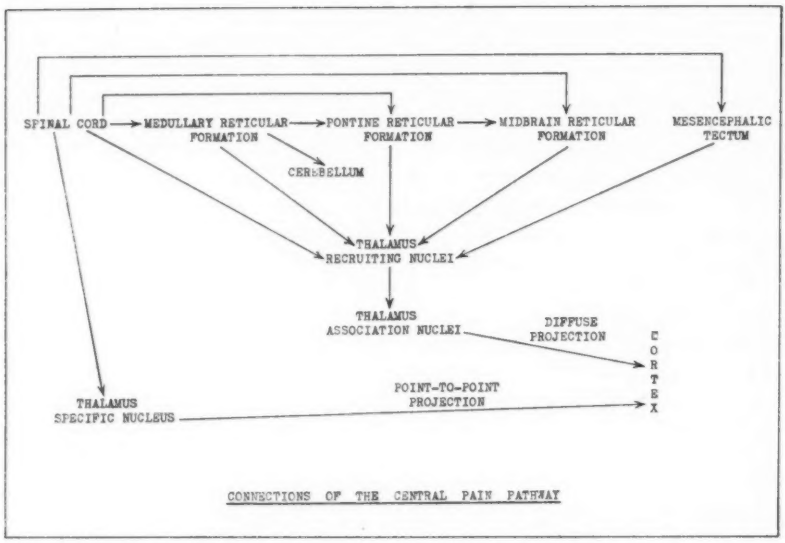

TEXT-FIG. 2.—Diagram of the connexions of the central pain pathway.

greatest cortical response in frontal areas. These observations may account for the success of prefrontal leucotomy (lobotomy) in cases of intractable pain; although the sensory awareness of pain, as mediated by the direct spino-thalamic pathway, is not abolished, the response to it is.

The operations of spinal or medullary tractotomy abolish pain of both types below the level of section, because in the spinal cord and lower medulla, all the central pain fibres are running together in the antero-lateral funiculus. However, rostral to the inferior olive, the spino-reticulo-thalamic fibres are medial to the direct spinothalamic fibres, so that in the operation of mesencephalic tractotomy, only the latter are cut. Walker (1942) reporting 3 cases of this type of operation, stated that diffuse pain was not abolished by the procedure. Reviewing these cases the following year, he (Walker, 1943) stressed the similarity between this type of diffuse unpleasant sensation and the painful crises of the thalamic syndrome. Both sets of fibres meet again in the centre médian, and intervention at this point abolishes both types of pain (Hécaen, *et al.*, 1949).

The most serious objection to the hypothesis that this spino-reticulo-thalamic system mediates diffuse pain is the supposed non-specific nature of the system. Starzl, Taylor and Magoun (1951) found that stimulation of both somatic sensory and auditory nerves in the cat evoked potentials in the brain-stem reticular formation. Amassian (1952) was able to

record from a single reticular neurone, and found that it was indifferently fired by stimulation of either the sciatic or auditory nerve. However, there is a fundamental difference in the anatomical organization of the central pain pathway compared with that of the medial and lateral lemnisci; in the case of fibres from the anterolateral funiculus, stem axons terminate in the reticular formation while in the case of the medial lemniscus, it is collateral branches which terminate in the reticular formation, there being no reduction in size of this fibre bundle between its origin and the specific thalamic nucleus. Thus the pain-conducting terminals in the reticular formation are different in nature, and perhaps greater in quantity than those of other sensory modalities.

In so far as it is possible subjectively to appreciate the "arousal mechanism" in intact man, it is common experience that a painful stimulus has a far greater arousing effect than any other modality of sensory stimulus. It is felt therefore that a quantity-dependent firing of the brain-stem reticular formation by the stem axons from the antero-lateral quadrant of the spinal cord may bring about a conscious feeling of diffuse, poorly localized pain or discomfort, and that this is compatible with the known functions of the reticular activating or arousal mechanism.

Summary

(1) The literature on the known connexions of ascending fibres in the antero-lateral quadrant of the spinal cord is reviewed.

(2) Four cases are described in which the diencephalon and brain-stem were examined for axonal degeneration, following successful tractotomy for the relief of pain.

(3) Terminal degeneration was found in the specific sensory nucleus of the thalamus of both sides, in the ipsilateral centre médian, and possibly in the anterior part of the ipsilateral thalamic reticular nucleus; in the nuclei of all four quadrigeminal bodies and ipsilaterally in the lateral reticular nucleus of the medulla oblongata. Massive bilateral terminal degeneration was found in the cells of the medial reticular formation of the medulla, and to a lesser extent in that of the mesencephalon and pons.

(4) The further connexions of the reticular nuclei concerned are reviewed and discussed.

(5) It is suggested that the direct spino-thalamic system is responsible for the type of pain that is immediately felt, sharply localized, and which lasts for only as long as the provoking stimulus is applied; while the spino-reticulo-thalamic system is responsible for diffuse, poorly localized pain or discomfort with an appreciably slower conduction time to consciousness, and which persists after the withdrawal of the initiating stimulus.

(6) It is shown that the two types of pain fibre run together below the

level of the inferior olive, and meet again in centrum medianum thalami. Surgical intervention at either of these two levels will be effective in abolishing both types of pain, but between the inferior olive and the thalamus it will not be.

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REFERENCES

AMASSIAN, V. E. (1952) *Fed. Proc.*, **2,** 5.
ARMSTRONG, J. A. (1950) *J. Anat., Lond.*, **84,** 146.
BRODAL, A. (1943) *Acta psychiat., Kbh.*, **18,** 171.
—— (1949) *J. comp. Neurol.*, **91,** 259.
BRUCE, A. (1898) *Brain*, **21,** 374.
BUCHER, V., and BÜRGI, S. (1945) *Confin. neurol., Basel*, **6,** 317.
BÜRGI, S. (1955) *Arch. Psychiat. Nervenkr.*, **194,** 67.
CHANG, H. T., and RUCH, T. C. (1947) *J. Anat., Lond.*, **81,** 150.
CLARK, W. E. Le Gros (1936) *J. Anat., Lond.*, **71,** 7.
COLLIER, J., and BUZZARD, E. F. (1903) *Brain*, **26,** 559.
DEJERINE, J., and ROUSSY, G. (1906) *Rev. neurol.*, **14,** 521.
DEKABAN, A. (1953) *J. comp. Neurol.*, **99,** 639.
EDINGER, L. (1889) *Anat. Anz.*, **4,** 121.
EVANS, D. H. L., and HAMLYN, L. H. (1956) *J. Anat., Lond.*, **90,** 193.
FRENCH, J. D., VERZEANO, M., and MAGOUN, H. W. (1953) *Arch. Neurol. Psychiat., Chicago*, **69,** 505.
GARDNER, E., and CUNEO, H. M. (1945) *Arch. Neurol. Psychiat., Chicago*, **53,** 423.
GEHUCHTEN, A. van (1901) *Névraxe*, **3,** 159.
GETZ, B. (1952) *Acta Anat.*, **16,** 271.
GLEES, P. (1946) *J. Neuropath*, **5,** 54.
—— (1948) *Acta anat.*, **6,** 447.
—— (1952) *Anat. Anz.*, **99,** 48.
—— (1953) *Acta neuroveg.*, **7,** 160.
——, and BAILEY, R. A. (1951) *Mschr. Psychiat. Neurol.*, **122,** 129.
——, and NAUTA, W. J. H. (1955) *Mschr. Psychiat. Neurol.*, **129,** 74.
GOWERS, W. R. (1878) *Trans. clin. Soc. Lond.*, **11,** 24.
HÄGGQVIST, G. (1936) *Z. micr-anat. Forsch.*, **39,** 1.
HANBERY, J., AJMONE-MARSAN, C., and DILWORTH, M. (1954) *Electroenceph. clin. Neurophysiol.*, **6,** 103.
HÉCAEN, H., TALAIRACH, J., DAVID, M., and DELL, M. B. (1949) *Rev. neurol.*, **81,** 917.
HENNEBERG, R. (1901) *Neurol. Zbl.*, **20,** 334.
HINES, M. (1955) *N.C. med. J.*, **16,** 239.

JOHNSON, F. H. (1953) *Anat. Rec.*, **114,** 327 (Abstract).
—— (1954) *Anat. Rec.*, **118,** 316 (Abstract).
KOHNSTAMM, O. (1900) *Neurol. Zbl.*, **19,** 242.
——, and QUENSEL, F. (1908) *Dtsch. Z. Nervenheilk.*, **36,** 182.
LASHLEY, K. S. (1954) *In:* Council for International Organizations of Medical Sciences. "Brain Mechanisms and Consciousness." Oxford, p. 52.
LEWANDOWSKY, M. (1904) *Denkschr. med. naturw. Ges. (Jena)*, **10,** *Neurobiol. Arb.*, Series II, **1,** 63.
MAGOUN, H. W. (1952) *Arch. Neurol. Psychiat., Chicago*, **67,** 145.
——, and MCKINLEY, W. A. (1942) *Amer. J. Physiol.*, **137,** 409.
MARSHALL, W. H. (1940) *Stain Tech.*, **15,** 133.
MAY, W. P. (1906) *Brain*, **29,** 742.
MEHLER, W. R. (1957) *Anat. Rec.*, **127,** 332 (Abstract).
——, FEFERMAN, M. E., and NAUTA, W. J. H. (1956) *Anat. Rec.*, **124,** 332 (Abstract).
MEYER, M. (1949) *Brain*, **72,** 265.
MORIN, F., and O'LEARY, J. L. (1950) *Anat. Rec.*, **106,** 226 (Abstract).
——, SCHWARTZ, H. G., and O'LEARY, J. L. (1951) *Acta Psychiat., Kbh.*, **16,** 371.
MORISON, R. S., and DEMPSEY, E. W. (1942) *Amer. J. Physiol.*, **135,** 281.
——, FINLEY, K. H., and LOTHROP, G. N. (1943) *J. Neurophysiol.*, **6,** 243.
MOTT, F. W. (1895) *Brain*, **18,** 1.
NAUTA, W. J. H. (1955) Personal communication.
——, and GYGAX, P. A. (1954) *Stain tech.*, **29,** 91.
OLSZEWSKI, J., and BAXTER, D. (1954) "The Cytoarchitecture of the Human Brain Stem." Basel.
PAPEZ, J. W. (1956) *Electroenceph. clin. Neurophysiol.*, **8,** 117.
PENFIELD, W., and BOLDREY, E. (1937) *Brain*, **60,** 389.
——, and JASPER, H. H. (1954) "Epilepsy and the Functional Anatomy of the Human Brain." London.
PETRÉN, K. (1901) *Nord. med. Ark.*, **34,** Afd. II, Nr. **14,** 1.
—— (1910) *Arch. Psychiat. Nervenkr.*, **47,** 495.
QUENSEL, F. (1898) *Neurol. Zbl.*, **17,** 482.
RIOCH, D. M. (1929) *J. comp. Neurol.*, **49,** 121.
ROSSI, G. F., and BRODAL, A. (1956) *J. Anat., Lond.*, **90,** 42.
——, —— (1957) *Arch. Neurol. Psychiat., Chicago*, **78,** 439.
RUSSELL, G. V. (1954) *J. comp. Neurol.*, **101,** 237.
RUSSELL, J. S. R. (1898) *Brain*, **21,** 145.
SÖLDER, F. von (1897) *Neurol. Zbl.*, **16,** 308.
SPILLER, W. G. (1905) *Univ. Pa med. Bull.*, **18,** 147.
STARZL, T. E., TAYLOR, C. W., and MAGOUN, H. W. (1951) *J. Neurophysiol.*, **14,** 479.
——, and WHITLOCK, D. G. (1952) *J. Neurophysiol.*, **15,** 449.
STEWART, P. (1901) *Brain*, **24,** 222.
THIELE, F. H., and HORSLEY, V. (1901) *Brain*, **24,** 519.
TOOTH, H. G. (1892) *Brain*, **15,** 397.
WALKER, A. E. (1938) "The Primate Thalamus." Chicago.
—— (1940) *Arch. Neurol. Psychiat., Chicago*, **43,** 284.
—— (1942) *Arch. Neurol. Psychiat., Chicago*, **48,** 865.
—— (1943) *Res. Publ. Ass. nerv. ment. Dis.*, **23,** 63.
WALLENBERG, A. (1899) *Neurol. Zbl.*, **18,** 829.
—— (1901) *Neurol. Zbl.*, **20,** 306.
WEBER, A. (1955) *Rev. Neurol.*, **93,** 817.
WHITE, J. C., and SWEET, W. H. (1955) "Pain, its Mechanisms and Neurosurgical Control." Springfield, Ill.
ZOTTERMAN, Y. (1933) *Acta med. scand.*, **80,** 185.

LEGENDS FOR PLATES

PLATE LXXXIII

(All figures impregnated by method of Nauta and Gygax.)

FIG. 1.—Terminal degeneration in ipsilateral thalamic n. ventralis postero-lateralis. Case 4. × 750.

FIG. 2.—Control: N. ventralis postero-medialis thalami, from same section as fig. 1. × 650.

FIG. 3.—Terminal degeneration in ipsilateral thalamic centre médian. Case 3. × 750.

FIG. 4.—Control: N. ventralis anterior, from same slide as fig. 3. × 650. This shows a good deal of granular artefact, but no true degeneration.

PLATE LXXXIV

FIG. 5.—Terminal degeneration in deep tegmental nucleus of mid-brain. Case 1. × 750.

FIG. 6.—Control: Dorsal tegmental nucleus from same section as fig. 5. × 650.

FIG. 7.—Terminal degeneration in N. giganto-cellularis at rostral medullary level. Case 1. × 750.

FIG. 8.—Control: N. ambiguus, from same section as fig. 7.

PLATE LXXXIII

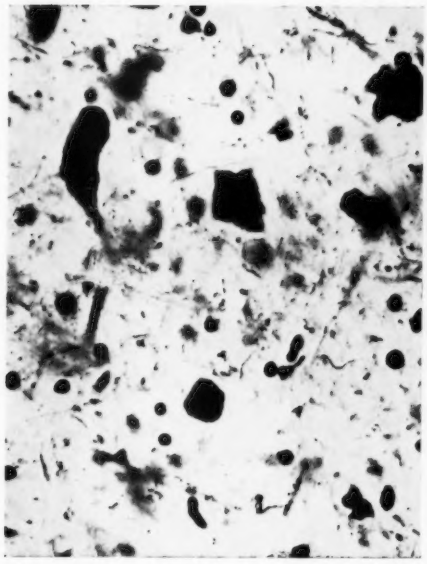

FIG. 1.

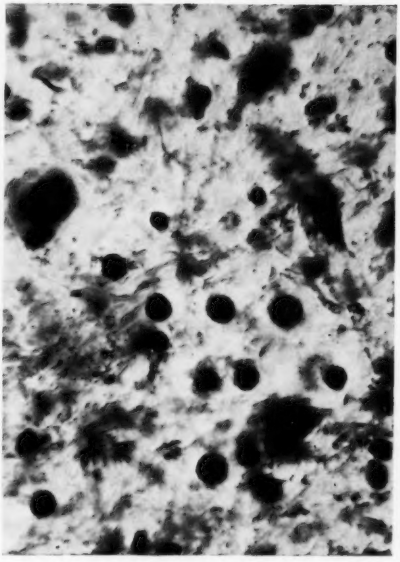

FIG. 2.

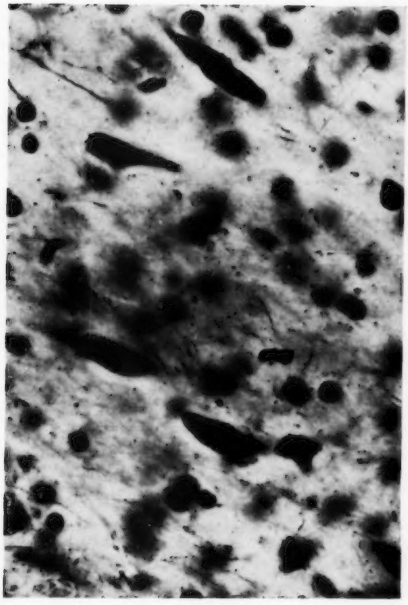

FIG. 3.

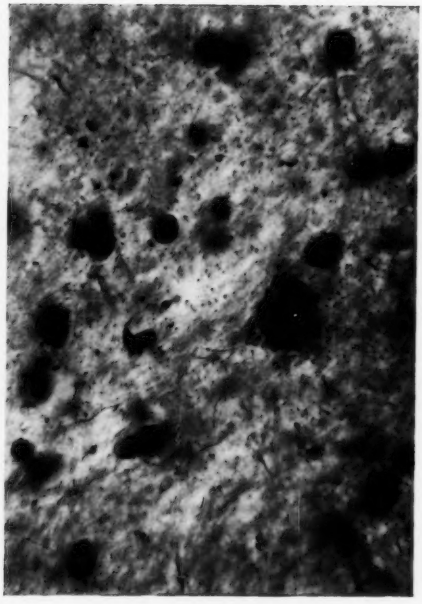

FIG. 4.

To illustrate article by David Bowsher.

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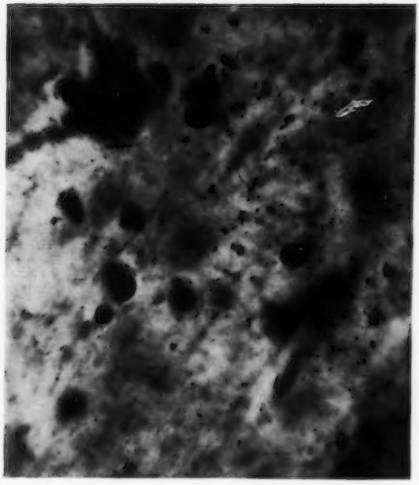

FIG. 5.

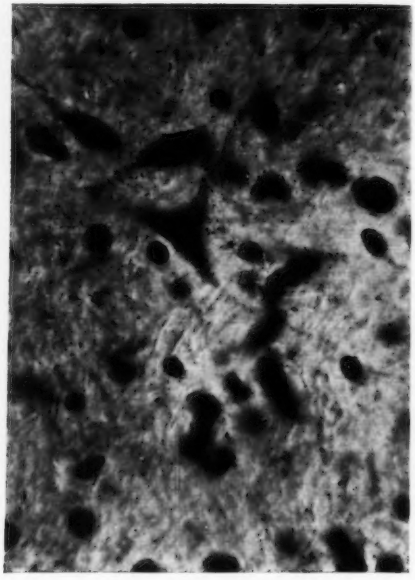

FIG. 6.

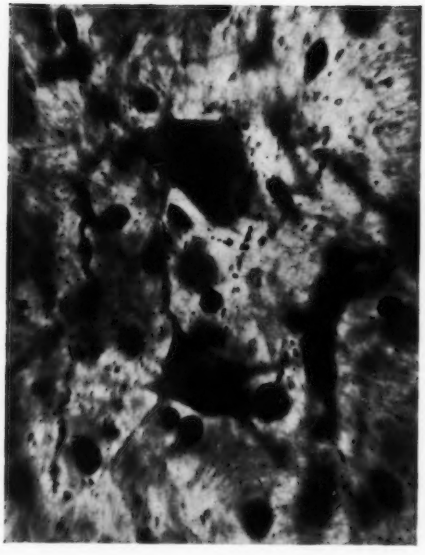

FIG. 7.

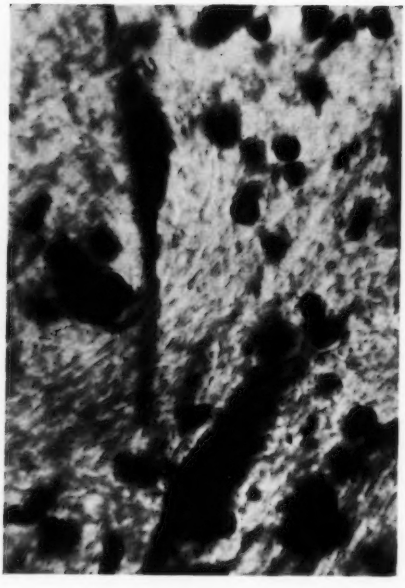

FIG. 8.

To illustrate article by David Bowsher.

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MUSCLE PATHOLOGY

An Atlas of Muscle Pathology in Neuromuscular Diseases. By J. GODWIN GREENFIELD, M.D., G. MILTON SHY, M.D., ELLSWORTH C. ALVORD, Jr., M.D., and LEONARD BERG, M.D. 1957. Pp. 104. Edinburgh and London: E. & S. Livingstone, Ltd. Price £2 5s.

The interpretation of muscle biopsies is at present one of the histopathologist's worst headaches. This is due partly to our lack of fundamental knowledge as to how the voluntary muscles react to various adverse conditions and, consequently, great uncertainty in correlating what is seen under the microscope with clinical assessments of muscle dysfunction. Indeed the specimen submitted may so closely approximate to the normal picture that it is difficult to reconcile with the story of gross disability. And if histological changes are recognizable how far are they representative of the affected muscles generally? The book does not exist that will smooth out these problems and the present volume is an effort to state them rather than to provide the answers. The authors have thus set themselves the task of defining and illustrating certain fundamental changes in the skeletal muscles with complete freedom from the bias conveyed by a clinical diagnostic label.

Part I is therefore devoted to an objective presentation of the histopathological reactions of muscle; brief descriptions of these are fully illustrated by photomicrographs of excellent quality, many of which are in colour and appear to be splendid reproductions.

Part II essays the correlation of changes with the clinical findings by means of rather elaborate tables. It is not altogether easy to glean the results of these analyses but, to quote the authors, "no single change has been found to be specific for any disease, and even combinations of changes are no more than highly suggestive." They have not found it possible to make any sharp histological distinction between primarily "degenerative" and primarily "inflammatory" conditions. The pathologist is in fact given no respite, and his road must still wind uphill. So he may agree with the authors when they sadly wonder (p. 96) whether the muscle biopsy is really helpful! Yet it must be hoped that time and further work will prove them right in forecasting that we shall eventually emerge from our present ignorance into a fuller understanding of muscle pathology. They have certainly pointed out a logical way whereby such knowledge may be amassed, and no serious student should neglect the present contribution which combines austerity with academic honesty.

DOROTHY S. RUSSELL.

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BRAIN ABSCESS

Der Hirnabszess. By Dr. G. WEBER. Pp. 188. Published by Georg Thieme Verlag. Price £2 12s.

This monograph is based on observations made during the years 1938–1955 in the neurosurgical department of Professor von Krayenbühl in Zürich. While all types of intracranial pyogenic conditions are surveyed, the chapter on abscess is, owing to its practical importance, by far the longest. Particular consideration is also given to thromboses of cerebral veins and sinuses and the problem of "otitic hydrocephalus" is fully discussed. In each condition ætiology, diagnosis and treatment share equal attention; extensive use has been made of the auxiliary investigations at the disposal of the modern neurosurgeon including E.E.G., contrast X-ray of ventricles, arteries and, occasionally, venous sinuses. The modifications on bacteriology and neurosurgical indication brought about by the antibiotics are explained in some detail.

While it does not, perhaps, reveal anything radically new, the book will nevertheless be of considerable interest to all workers in this field who will draw advantage from the author's wide experience and balanced conclusions. It is written in a lucid and readable style, and it should carry added weight as a document coming from a distinguished department. A comprehensive list of references testifies to the author's wide reading; it will be noted that British contributions to the subject have been given very adequate consideration.

A. MEYER.

AUTONOMIC NERVOUS SYSTEM

Autonomic Nervous System. British Medical Bulletin, Vol. 13, No. 3, September 1957. Price 20s.

This number contains thirteen essays on the chemical and electrical physiology of the autonomic system, related to its structure and function. All the contributors are, at present, actively engaged in physiological research so that the volume comprises a most valuable and virtually complete précis of present knowledge of the nature and purpose of cholinergic transmission and the neuronal control of viscera.

DENIS WILLIAMS

ELECTRODIAGNOSIS

Electrodiagnosis qnd Electromyography. Edited by SIDNEY LICHT, M.D. 1956. Published by Elizabeth Licht. New Haven. Price $10.

This book, which contains contributions from twelve physicians and neurophysiologists, should be of considerable help to those engaged in clinical electrodiagnosis.

An historical introduction is followed by a chapter on apparatus by Rogoff, and on the physiology on skeletal muscle by Fischer. Conventional techniques of muscle stimulation are fully covered by chapters on motor points (Walthard and Tchicaloff), routine electrodiagnosis (Oester and Licht), chronaxie (Harris) and strength-duration curves (Wynn-Parry). Progressive

or slowly rising currents are not often used in this country except in the examination of patients with hypocalcæmia, but a number of foreign papers have been devoted to this subject, and these are well reviewed by Liberson.

In the chapter on electromyography by Rodriquez and Oester the technique of needle sampling is adequately presented, although the illustrations could be improved both in number and quality. There is no mention of techniques involving nerve stimulation combined with electromyographic recording, an omission which gives this section a slightly old-fashioned air.

In his preface to the book, Dr. Licht states that it was assembled "for physical medicine physicians, since they have evolved as the logical specialists to conduct these tests." Those neurologists who are illogical enough to do their own electrodiagnostic work will also find much to help and interest them in its pages.

R. W. GILLIAT.

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